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THE ALLERGIC DIATHESIS: AN INFECTIOUS DISEASE?

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IN 1773, Blackley in reviewing the opinions of his time as to the cause of hay fever says "Upon one point, however, all authors agree *viz.* on the existence of some peculiarity of the constitution which predisposes to the disease." In our own day, this opinion is still held by practically everyone, and no serious consideration is given to any alternative.

The idea that the allergic diathesis disorders, hay fever, asthma, vasomotor rhinitis and atopic eczema, may be the result of an infectious disease seems at first thought preposterous. Actually, we do not know the cause of the defect we call the allergic diathesis, and there is no real reason why the possibility of an infectious disease transmitted largely within the family should not be considered. There is solid evidence from many studies[1-13] that the disease is passed from one to another within the family, but the role of heredity as the mode of transmission has been questioned occasionally, particularly by Ratner and by Kabat. [11,12] The only reason for not considering the possibility of contagiousness has been the difficulty of picturing how an infectious agent could produce the clinical disease. This problem arises partly from confusion between laboratory allergy with its clinical counterparts and the diseases associated with the allergic diathesis in man. Clinical allergists have often tried to explain why they feel that they see something different from laboratory allergy but have always had disagreements over what should be included as diathetic allergic diseases. A statistical study by Schwartz[13] of the diseases found in the families of asthmatic patients gives better grounds than we had previously for separating vasomotor rhinitis, allergic rhinitis, intrinsic asthma, extrinsic asthma and infantile eczema as

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disorders transmissible as a group, within the family, unrelated to other allergic diseases. In addition these disorders occur together or in sequence in the same patient so that it is possible to describe a natural history as though they were one disease. An effort will be made later to describe this disease in detail and to suggest that plausible working hypotheses on the grounds of infection can be advanced.

First, a study of the family histories and close contact histories of 432 patients will be presented.

MATERIALS AND METHODS

The private patients coming to the Allergy Department at the State University of Iowa present an unusual opportunity to study a stable population whose few close contacts are mostly either relatives or others from the same locality. The majority of the patients seen in our clinic come from rural areas or very small towns. A few patients are from Iowa City which is a university community. Not only does this situation lend itself to the study of the epidemiology, but exposure to abundant mold and ragweed gives rise to a relatively large number of patients with a characteristic pattern of symptoms recognizable by history alone.

The study includes every new private patient with the allergic diathesis seen by the author over a period of two and one-half years. These total 432, and for the purposes of discussion they and 282 control subjects will be divided into five groups as follows:

Group I: 216 patients whose parents, aunts, uncles or grandparents had one or more of the allergic diathesis conditions.

Group II: 174 patients who had none of these relatives with the disease. (For the purpose of this study, negative family history means absence of antecedents and, therefore, does not include children, siblings, or parents who developed the diesase after the patient.)

Group III: 42 patients with siblings, only, affected.

Group IV: 19 patients omitted from the study.

Group V: 282 control subjects.

Diagnosis.—There were 219 patients with asthma and 211 patients with nasal symptoms alone. Two patients had atopic eczema without respiratory symptoms.

The diagnosis of asthma was made on clinical grounds and skin tests were done on all patients. With the exception of two men who also had severe emphysema, the cases were entirely typical of intrinsic, extrinsic or mixed forms of the disease.

The grounds for diagnosis in those with nasal disease were as follows: Eighty-two patients had pollen allergy with appropriate positive skin tests; twenty-three had house dust allergy with marked positive skin tests; sixty-two had mold or milder house dust sensitvity. With mold sensitivity the symptoms were more severe in the summer but there were perennial symptoms

associated with house dust sensitivity or handling of feed in most of the mold-sensitive patients. These patients had moderate or marked reactions to molds, house dust or both and membrane changes characteristic of allergy. Thirty-four patients had nasal polyps with associated vasomotor rhinitis. These individuals often had small skin reactions to house dust and mold or, much less commonly, to animal danders. Many such patients had difficulty with farm dusts and house dust but were also extremely susceptible to secondary factors such as irritants and weather changes. Ten patients had miscellaneous primary allergies, such as animal danders and flour. These sensitivities were confirmed by skin tests.

All the patients with nasal disease were seen by the Ear, Nose and Throat Department as well as by the author.

Contact Histories.—Contact histories were taken on all patients who gave a negative family history. After about 200 consecutive cases had been seen and the data was analyzed for the first time, it became evident then that the family history findings were quite unlike previous urban studies. From that time on, the date of onset in affected relatives was recorded.

Two types of contact were accepted as "positive contact history." The first was termed "living with" contact which included roommates, step parents, spouses, and the like. The second was designated as "very close" which included relationships, such as "best girl friend" where considerable personal intimacy was involved, or work situations—such as two high school students who worked after school every day for neighbors incapacitated by asthma.

The method of obtaining the control group is described with the control data.

RESULTS

Group I.—Patients with a positive family history of the allergic diathesis diseases.—There was a striking relationship between the presence of the disease in parents or close relatives and early onset of the disease in the families' children. Altogether, 187 patients were seen whose symptoms had appeared before they were ten years old. Of these, 148 had parents, aunts, uncles or grandparents with allergies. Fourteen had siblings affected, and twenty-five knew of no family history of the disease. Including the fourteen with siblings affected, 87 per cent of those who were under ten when their symptoms began had the disease in their family.

If the ninety-four children who were seen with their parents are considered separately, 91 per cent had the disease in their family and 96.8 per cent had the disease either in their family or in very close contacts. Only three patients had no known close contact with the disease and of these, two had parents who complained of "a lot of sinus trouble." The remaining one belonged to a household in which there had been a succession of student roomers who did baby sitting.

In other words, the disease was rare in children who had no known exposure to it.

Because this was out of line with the experience of others in urban studies, 100 charts of my colleagues' patients of all ages whose symptoms had appeared before they became ten years old, were pulled in alphabetical order from this year's general clinic file. There were only thirteen patients with a negative family history.

TABLE I. THE RELATIONSHIP OF SEX TO AGE AT ONSET OF SYMPTOMS

	Male	Female
Family history—positive		
Age at onset under 20	85	90
Age at onset over 20	14	27
Family history—negative		
Age at onset under 20	23	15
Age at onset over 20	87	49

Most of the author's patients who began their symptoms in the first decade experienced them by the age of six. Eighty-two per cent of all the patients with a positive family history had developed symptomatic disease by the age of twenty. Only fourteen men and twenty-seven women began their symptoms after twenty. In other words, of ninety-eight men who developed the disease after twenty years of age, only fourteen had had the disease in their family.

The relationship of sex to age-at-onset in the family-history-positive and family-history-negative groups is shown in Table I. Some of the patients whose disorder began as adults had experienced their illness after that of relatives who had developed the disease a few months or years before them. One patient had an asthmatic grandfather whom she had never known but had developed asthma three years after her marriage to a farmer who shared the farm of his asthmatic father. They adopted a child who also developed asthma. Thus, while there were undoubtedly some patients who had significant symptoms for the first time years after early association with other members of their allergic family these cases were much less common than had been anticipated from previous urban clinical impressions.

The unbroken line in the graph in Figure 1 shows the number of patients with a positive family history who developed initial symptoms in each decade. It can be seen that the number of cases with a positive family history drops sharply by the age of twenty.

The relationship of the nearest affected relative is set forth in Table II. Parents had the disease in 151 cases. Grandparents were no longer reported as the only affected relative after the patient had reached an age when grandparents would be expected to be dead and, therefore, not in contact

with the patient. One hundred and sixty eight patients had more than one close relative with the disease.

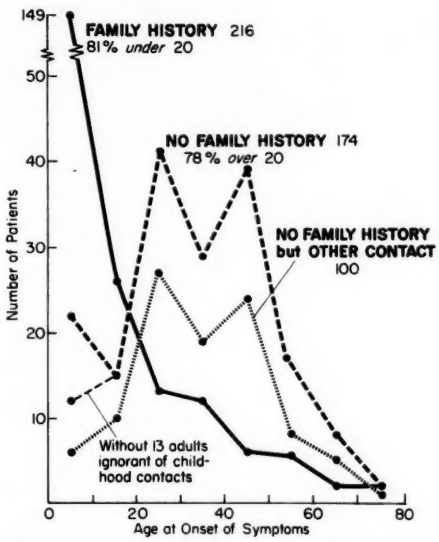

Fig. 1. Number of patients with a positive family history who developed initial symptoms—by age in decades.

Group II.—Patients with no family history of the allergic diathesis. The relationship of age at onset to the finding of a negative family history is shown in the graph in Figure 1. Seventy-eight per cent of these patients experienced their symptoms after the age of twenty. Below the heavy broken line (Fig. 1) which represents the patients with a negative family history, is a lighter broken line which designates the proportion of these patients who were able to give a history of living with or of having very

TABLE II. PATIENTS WITH A FAMILY HISTORY OF THE ALLERGIC DIATHESIS
(Age at Onset of Symptoms and Nearest Relative Affected)

Age at Onset	Total in Age Group	Mother	Father	Both	Grand-mother	Grand-father	Aunt or Uncle	Sib Only*
0-10	149	54	43	8	19	10	15	14
10-20	26	8	4	2	4	2	6	9
20-30	13	3	7	0	1	1	1	1
30-40	12	2	2	3	1	2	2	8
40-50	6	3	0	3	0	0	0	2
50-60	6	2	3	0	0	0	1	11
60-70	2	1	1	0	0	0	0	7
70+	2	1	1	0	0	0	0	0
Total	216	74	61	16	25	15	25	42

*Not included in "total in age group."

TABLE III. THE RELATIONSHIP OF PATIENTS TO NON-FAMILIAL CONTACTS

Age at Onset	Total in Age Group	Negative Contact History	Positive Contact Total	Areas of Doubt in Negative Contact Group	Nature of Contact*	Time until Onset of Symptoms
0-10	23	17	6	2 rooming house 3 parents "sinus" 7, 50+ no informant available 6, 20+ no informant available	1 aunt in-law with hay fever 1 asthmatic roomer in his home 1st 15 yrs. of his life 1 asthmatic step grandmother lived with for 6 months 2 cousins with allergy on the non-related side of family 1 great granduncle with asthma lived close, "loved him up a lot"	2 or 3 years Under 5 years About 1 year Under 10 years About 2 years
10-20	15	5	10	1 mother "sinus" 1 sister "sinus"	1 spouse 1 aunt in-law and her son and 2 school pals with asthma 1 uncle in-law lived with when parents away 1 lived in home of asthmatic uncle in-law for 2 years 1 worked daily after school for incapacitated asthmatic farmer 1 worked daily after school and vacationed with asthmatic woman 1 best girl friend and patient spent all summer together 1 best girl friend and constant companion asthma 1 roommate in boarding school	1 or 2 years Predating Predating 2 or 3 years About 3 years 2 years About 2 years About 3 years About 1 year
20-30	41	14	27	1 knows little of father who died in her childhood 1 developed the disease in the Army 1 mother "chronic laryngitis" 2 began symptoms shortly after discharge from Navy 1 among many roommates 1 sister "severe sinus disease" 2 were more than 70 and began symptoms long ago	6 spouses 1 lived with husband's brother and his asthmatic child, her own child developed asthma and then herself 1 wife's brother, hay fever 1 wife's sister has asthma. His own father who came to stay in old age developed asthma also 1 wife's father asthmatic 1 shared small office with a man with severe hay fever 1 nurse on medical wards during pregnancy. Symptoms developed after delivery 1 general hospital dentist. Dental care to asthmatics among others 1 MD, anesthetist 1 husband's boss's family have several allergic children who are "at their house all the time" 1 baby sitter sat for asthmatic child 2 to 3 times weekly, 2 years 1 nurse on medical wards. Her mother came to stay with her and developed asthma after about 8 mouths 1 child with predating symptoms 1 best girl had severe hay fever sitting under trees in spring 1 MD, internal medicine, developed hay fever during residency 4 roommates 2 next door neighbor families. Much day-to-day interchange 1 girl's best friend and her family	Under 10 years 2 years Predating Under 10 years Under 10 years 3 years 1 year About 2 years Patient contact under 6 years About 3 years 2½ years Nursing under 5 years Predating Hay fever following spring Patient contact under 5 years 1 to 3 years 3 to 5 years Predating

Age at Onset	Total in Age Group	Negative Contact History	Positive Contact Total	Areas of Doubt in Negative Contact Group	Nature of Contact*	Time until Onset of Symptoms
30-40	29	10	19	2 children. Date unknown	9 spouses	Up to 15 years
				1 industrial compensation	4 predating children	Predating
				1 wife "sinus"	2 wife's sister's husband has severe hay fever. Patients, both husband and wife have allergic rhinitis	Under 5 years
				1 70+	1 wife's sister asthmatic	Predating
					1 wife's brother has hay fever, visits 2 times weekly. His wife probably has allergic rhinitis too	Predating
					1 husband's sister asthma	Predating
					1 husband's asthmatic sister lived with them all summer for 2 years	2 years
40-50	39	15	24	3 children. Date unknown	6 spouses	Predating
				4 wife "sinus"	1 sister in-law asthma	Predating
					1 brother-in-law asthma	10 to 15 years
					1 brother-in-law severe hay fever	Predating
					1 sister-in-law and daughter of this woman	Predating
					1 son's wife hay fever and son has developed hay fever since marriage	2 years
					1 grandchild asthma. Considerable contact	About 4 years
					1 shares farm and chores daily with asthmatic neighbor	5 or 6 years
					1 worked side by side daily and went camping	4 years
					2 roomers	2 and 3 years
					6 predating children. Both parents affected in one instance	2 to 15 years
					1 stepdaughter asthma	About 4 years
					1 brother-in-law hay fever	Predating
50-60	17	9	8	1 wife "sinus"	1 spouse	About 1 year
					1 wife's mother and 3 of his children	15 years
					1 daughter-in-law hay fever	Predating
					1 son's wife and grandchild	Predating
					1 son's wife and grandchild	About 4 years
					1 nurse in small hospital. Two other nurses and a nurses' aid have asthma	Predating
					1 son has hay fever and wife coughs constantly	Predating
					1 grandchild asthma	Predating
60-70	8	3	5	1 wife and daughter "sinus"	2 spouses	(About 15 years About 1 year)
					2 children with predating symptoms	20 to 30 years
					1 brother-in-law and niece	Predating
70+	2	1	1		1 spouse, husband asthma	2 years

*All in-laws included in this table had "living with" or "very close" relationship to the patient.

TABLE IV.
COMPARISON OF CONTACT RATES IN PATIENTS AND TWO CONTROL GROUPS*

Age by Decade	A Allergy Patients		B Mixed Controls		C Patient Controls	
	Total in Age Group	Close Contact Positive	Total in Age Group	Close Contact Positive	Total in Age Group	Close Contact Positive
0-10	23	6	0	0	23	1
10-20	15	10	6	2	15	4
20-30	41	27	29	8	41	12
30-40	29	19	23	5	29	8
40-50	39	24	31	7	39	10
50-60	17	8	14	4	17	6
60-70	8	5	5	1	8	3
70+	2	1	0	0	2	1
Total	174	100	108	27	174	45

p_1=per cent with contact.
p_2=per cent without contact
$t = p_1 - p_2 = > 6$, which is highly significant

$$T = \sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}}$$

*The author would like to acknowledge the help of Dr. L. A. Knowler in checking the significance of these observations.

TABLE V. THE RELATIONSHIP TO CONTACTS IN PATIENT AND CONTROL SUBJECTS

Relationship	Patients	174 Non-Allergic Control C Subjects
Spouse	26	8
Offspring	15	4
In-law	23	9
Stepchild or parent	2	1
Nephew	0	2
Offsprings' spouse and grandchildren	4	
Roommate	5	3
Roomer	3	0
Work or friend	20	15
Cousin (with allergy from the non-relative parent)	2	3
Total with positive contact	100	45
Total living with contact	(54)	(18)

close contact with a non-relative who was affected with active allergic diathesis symptoms. One hundred patients in the negative family history group recorded this type of history. When specific dates could be obtained, it was found that the illness had usually developed between six months and five years after the affected contact had been associated with the patients. The largest number of patients reported two to three years. Table III gives details of the contact histories, and Tables IV and V compare this data with those gathered from the control populations. Table VI shows the disease described in the contact patients.

The large number of cases in which the disease occurred after marriage to a spouse who had respiratory allergy is highly significant. Of the 109

patients who developed the disease between the ages of twenty and fifty, twenty-two had experienced their symptoms after their marriage to someone who was afflicted with it. The expected rate would be, at the most, two or three. The number in the control series is seven. This number represents an indication of the possibility of a non-allergic subject marrying someone with the disease. The number does not include the possibility of the non-allergic subject not only marrying someone with the disease but also developing it himself within a few years of such a marriage. This chance is of course much smaller. If the same argument is applied to the rest of the contact data, one must consider not only the chance of having an

TABLE VI. MANIFESTATIONS OF THE ALLERGIC DIATHESIS IN PATIENTS AND THEIR CONTACTS

Patient's Disease	Disease in Contact						
	Asthma Family Contact	Asthma Other Contact	No Contact	Allergic Rhinitis Family Contact	Allergic Rhinitis Other Contact	Eczema Family	Eczema Other
Asthma	103*	35	36	19*	21	2	3
Allergic rhinitis	50*	13	38	44*	31	0	1
Total	153	48	74	63	52	2	4

Total positive contact 316 or 77 per cent of all patients exclusive of siblings. If siblings are included as positive contact, 83 per cent of all patients have positive contact histories.

extremely close relationship with a person who has asthma or hay fever but also the chance of doing so and being included in the 1 per cent of the adult persons expected to develop the disease within a decade. This double coincidence would be much less frequent. The error in the control material presented would have to be immense to invalidate the conclusion that contact is a determining factor in the development of this disease.

Group III.—Patients with siblings only affected. There were forty-two patients whose only family history of the disease was in siblings. Many of the older patients among this group had difficulty in remembering whether they or their siblings had developed the disease first, and they were not able to remember much about their siblings' contacts. Several of the younger patients could give a history of a common contact with the disease, but it was decided to keep this group separate because of the difficulties with the group as a whole. The ages at onset of patients with siblings only affected are set forth in Table II.

Group IV.—Patients omitted from the study. There were five patients who could not be included because they were adopted or for various other reasons knew nothing of their family. Fourteen patients who may have had the allergic diathesis and *did* have a negative family history were rejected. In these, the diagnosis was difficult because of mildness of the disease,

excessive infection or vasomotor rhinitis from the use of nose drops. These patients were equally divided as to positive or negative contact histories.

Group V.—Control subjects and estimate of local incidence. Many surveys have been made in an effort to assess the incidence of the "hay fever-asthma" group of diseases. About 10 per cent is the usual estimate quoted, but the figures vary from Ratner's[13] 10 to 19 per cent in 3,000 medical students, nurses and physicians to 4.8 per cent among 115,000 persons included in an interview study conducted by the U. S. Public Health Service in 1957-58.[26] None of these published statistics are from Iowa. A door-to-door census was taken last year by interviewers under the direction of H. T. McCorkle[27] of the State University of Iowa Institute of Agricultural Medicine. These interviews included the members of 118 farm households and 150 households in Iowa City, a university community with a population of 36,000. A total of 935 people were included. The farm families showed an incidence of 10 per cent, and 11 per cent of the city people were affected. These samples are relatively small, but they probably give some indication of the incidence. In spite of the abundance of allergens, this figure does not differ greatly from many urban estimates.

Two groups of people in the hospital and adjoining medical school were interviewed by the author in an attempt to determine the expected rate of very close contact with respiratory allergy sufferers among those without the disease or a history of it in their family. At first, 108* non-allergic, negative family history men and women, who corresponded in sex and in age and age at onset of symptoms in the adult allergic patients with a negative family history, were questioned. It was felt that the employees, although largely drawn from rural areas, might be selected in a different manner from other patients. Therefore, another group (including children) was questioned. A room-to-room canvas was made in the private wing, and people in private patient waiting rooms other than that for otolaryngology were questioned. The need for fifteen more children was filled by W. B. Anderson of the Department of Pediatrics who questioned the parents of fifteen consecutive non-allergic negative family history children. The results of questioning these two groups are given in Table IV. The close contact rate was similar in the two sets of controls. It was almost 25 per cent except in the pediatric cases where the rate was much lower. Table V summarizes these findings.

There may be some difference in rapport between one's own patients and people questioned at random. However, all the questioning except for that of the fifteen children was carried out by a single observer, the author. Most people were responsive to the idea that they must think and answer carefully because of the nature of the research. There can be no doubt

*This corresponded to the number of patients at the time when the first control group was questioned.

that patients who have a disease become more conscious of it in others. In dealing with very close contacts such as marital partners, however, this awareness should not be a major factor. On the other hand, patients, like everyone else, have been taught that the disease is not contagious, so that there is sometimes considerable resistance to answering questions which implicate a contagious factor. As the study continued the author accepted negative answers less readily, particularly in those patients in whom the disease was of recent origin. Pressure exerted by the interviewer does produce an increase in positive answers so that there is a problem as to the degree of objectivity in questioning in the control groups. Every effort was made to be equally objective with both groups.

There were significantly more allergic patients who had close contact than non-allergic patients with close contact. No explanation is offered for the absence of the disease in non-allergic patients with close contacts; some may yet develop symptoms however and others may continue to be immune.

DISCUSSION

From the data presented, it appears that the disease developed most often from one to five years after the birth of a child into an affected family or from one to five years after a non-allergic subject with no family history of the disease had close contact with someone suffering from the disease. A smaller number of patients developed symptoms in the next five-year period and from then on there were only occasional cases. It was common for others in the family to be affected within a few years of the first case (there seemed to be a secondary attack rate). This is of considerable interest because it resembles the incidence pattern observed by Piness and Miller[25] in a study of two new company towns, and also by Fine and Abram[28] and Shilkret[29] in their studies of the development of ragweed hay fever in immigrants. All these authors have been surprised to find that from 65 to 77.5 per cent of their cases occurred in persons who had had no previous sign of the disease and whose families were free of it. (In other words, from the point of view of the present study, they occurred in the non-immunes). Piness and Miller[25] also noted that of their 171 cases (seventy-one adults with a negative family history) the disease occurred in both husband and wife in thirteen instances; six couples having no family history of these disorders and seven having a unilateral history. This, like our observation, is well outside the expected number of such coincidences.

The fact that children rarely developed the disease unless they had known close contact with it is difficult to explain away on the grounds of heredity even though 91 per cent had close relatives with the disease. This figure is much higher than those reported in several extensive surveys of family history in large urban centers, such as London, Copenhagen, New York and Chicago.[1,12,13] In approximately 50 per cent of the hospital clinic patients in these studies under the age of ten, a negative family history was re-

corded. Feinberg[9] states that while almost half of his clinic patient children in Chicago have a negative family history, his private patients have about 25 per cent negative histories. He attributes this difference to intelligence in reporting, but it might well be explained by differences in crowding. Intelligence is not likely to be the factor in the Copenhagen study,[13] because Schwartz personally visited all the living close relatives of his patients. The difference between these figures and ours might reflect a relatively high manifestation rate or recognition rate, but it seems unlikely that the patient without antecedents, who accounts for 50 per cent of the city figures, should almost completely disappear. This is particularly true since the total incidence in our area does not seem to be greater.

Adopted children were not specifically asked about except where the patient himself was the adopted child. Three patients mentioned that they had adopted children who had developed the disease. One of these patients who belonged to a family with many affected members had adopted two children in infancy from different sources both of whom have since developed asthma or hay fever.

REVIEW OF PRESENT KNOWLEDGE OF THE DISEASE

Taken altogether these observations make it necessary to review what we know of the allergic diathesis to see whether an infectious cause is really inconceivable.

*The Natural History and Pathology of the Allergic Diathesis**

General Considerations: The allergic diathesis is chiefly a disease of man. Disorders that may be similar do occur in the dog and cat and perhaps in cattle.

It is customary to divide the allergic diathesis disorders into an extrinsic group (implying reaction to outside allergens) and an intrinsic group (implying reaction to internal allergens, usually thought to be bacteria or their products). The first group includes hay fever, allergic rhinitis and extrinsic asthma while the second includes vasomotor rhinitis and intrinsic or so called "infective" asthma. In Europe, intrinsic asthma is often referred to as non-allergic asthma because, although the exacerbations are associated with bacterial infections, the existence of any bacterial allergen has never been proved. American allergists have been inclined to assume that allergy must exist, because it is demonstrated in the extrinsic asthmas which, both in family transmission and in other ways, appear to be one with intrinsic disease. These two classes are seen in all combinations. For purposes of description, the term intrinsic will be used to describe those cases with negative skin tests and with symptoms brought on by infection and associated with a characteristic hypertrophic nasal

*The name "allergic diathesis" will be used in spite of the contradiction in terms between diathesis and disease. Ratner has suggested the name "allergic respiratory cutaneous syndrome," but this is cumbersome, moreover, a new name is distracting.

and sinus pathology without intending to imply bacterial allergy as a proven factor.

Clinical Course: Initial symptoms of the allergic diathesis may begin at any time of life. Their nature is considerably influenced by the age at which the disease first shows itself. Infantile (atopic) eczema begins most often in infancy and childhood. The extrinsic allergies are much more common in the younger patients. High degrees of sensitivity as measured by skin test are seldom seen in patients whose first symptoms occur after they are thirty. The intrinsic disorders are common in the adult but may occur at any age. Infants, small children and pregnant women are more susceptible to the disease than others. (This refers to onset, not effect, on the already present disease).

If the disease begins in infancy, it generally begins after two months of age or after weaning. It may take the form of eczema, asthma or rhinitis. The onset is most frequent in the fall, winter and spring and there is often an accompanying respiratory infection.

The skin lesions of eczema are small, very itchy blisters, which break down with subsequent crusting and, in chronic cases, lichenification of the skin. Hemolytic staphylococci or hemolytic streptococci can frequently be cultured from infantile eczema lesions.[14]

When serum is taken from an eczematous child for passive transfer tests, antibodies to milk, egg white and other foods (usually several) are found, but elimination of these foods *often* has no effect upon the lesion and has been given up by many dermatologists. Thus, although the allergy may sometimes aggravate the eczema, the antibody seems to accompany this lesion rather than to cause it directly. Other symptoms such as asthma or urticaria, directly related to the sensitization may occur. About 60 per cent of infants with this infantile eczema develop asthma or nasal symptoms before five years of age.

The rest of Schwartz's[13] allergic diathetic group are respiratory disorders (vasomotor rhinitis, allergic rhinitis, asthma) and often begin after acute respiratory infections; for example, measles, influenza, streptococcal sore throat, whooping cough or pneumonia, or after accidental exposure to a damaging irritant. Spontaneous remissions and exacerbations are characteristic, particularly of the patient with extrinsic allergies.

When the disease begins in the young and is largely activated by outside allergens, it may gradually improve with age, and children are often said to grow out of their asthma or hay fever. This can never be predicted with any certainty. The patient's tendency to become sensitive appears to vary from time to time. Thus, while the majority of patients sooner or later develop some degree of sensitivity to constantly present "good allergens" such as house dust and feathers, seasonal allergies vary much more from individual to individual. It is as though activation of the sensitizing process

and exposure to the allergen have to coincide. When the onset is later in life, there is a tendency for the patient to be less skin sensitive and for the disease to be more infection-dependent. In addition, those whose disease continues from childhood beyond middle life tend to become chronically infected by bacteria in the respiratory tract. They develop more and more the pathological and symptomatic characteristics of the "intrinsic" disorders.[15] Judging by the literature, climate affects the manifestations, for the intrinsic forms are extremely common in England and relatively few in California. Complete remission becomes less frequent in patients who develop polyps, hypertrophic changes and a great deal of chronic bacterial infection. In general, skin sensitivity is in inverse proportion to hypertrophic changes in the nasal and sinus membranes at any age.

Symptoms and Lesions: The characteristic picture in the nose is one of obstruction and non-purulent rhinorrhea with pale bluish or dusky pink swollen membranes. There may be irritation of the eyes and watery rhinorrhea, particularly if seasonal or intermittently met allergens are involved. In the more chronic year-round either intrinsic or extrinsic conditions, nasal obstruction is often the chief complaint. The swelling represents both edema and proliferation; the latter is more prominent in those with chronic vasomotor rhinitis, polyp formation and hypertrophic sinusitis. Eosinophils are numerous in the affected membranes and sometimes can be found in nasal smears. The surface epithelium of the polypoid tissue shows areas of necrosis.

Asthma develops when the lower respiratory tract becomes involved. Often a patient with nasal allergy, polyps or vasomotor rhinitis develops asthma for the first time after being afflicted with influenza or some other chest infection. The disease is characterized by bronchospasm and a peculiar tenacious mucus which, particularly in the intrinsic asthmatic, may be so gelatinous that plugs of it completely obstruct portions of the airway. The mucus glands hypertrophy as do the bronchial muscles, and during active phases of the disease, the bronchi become edematous and inflamed, adding to the obstruction. The bronchospasm of asthma is aggravated by anything which stimulates the respiratory reflexes. *While the disease is active* as a result of infection or exposure to allergens, such stimulae as irritants, coughing, laughing, sudden changes in weather, drafts or emotional upset may act as triggers for the individual attacks. Asthma is often more severe at night even though the heavier exposure to the allergen may be in the day time. The reasons for this are not understood. Changes in fluid and electrolyte balance seem to have some effect upon the symptoms and physiological changes in these may play a part in aggravating the condition at night.

The Effect of Treatment: When allergy is the prime activating factor the manifestations can be lessened by removal of the allergens from the

environment or by repeated subcutaneous injections of the offending allergens. The mechanism by which these injections produce their effect is uncertain, but may be the result of the formation of blocking antibody (a gamma globulin "bipolar" type antibody, capable of agglutinating red cell to red cell, for instance). Whether or not a specific allergen is involved, the symptoms can be alleviated by adrenocortical hormones and are modified by iodides as well as other expectorants and a variety of antispasmodics and sedatives. X-ray therapy and sometimes blood transfusion or sera from other subjects may produce at least temporary remission. In some patients, particularly those with intrinsic asthma, a curious violent, sometimes fatal, respiratory reaction to aspirin may occur. This differs from the urticarial angioedema type of reaction seen in non-allergic diathesis patients in consisting solely of acute respiratory symptoms. In both the intrinsic and extrinsic disease, treatment of bacterial respiratory infection may produce dramatic improvement.

The Relationship to Allergens: The allergens involved in these diseases are not particularly good antigens when injected into animals or human beings, and we do not know why they are "good" sensitizers for the allergic diathesis victim.

The reaction to the allergens is, except for rare cases, a local one which occurs in the respiratory membranes unless the allergen is injected. Injection of an extremely small amount of the antigen may cause a generalized reaction. Such reactions seldom occur in the natural disease. For example, in contrast to the patient with a bee sting sensitivity, the patient with ragweed hay fever need have no fear of acute anaphylaxis while going for a walk in the country in August even though he may be perfectly miserable with rhinorrhea. The reason for the localization of the symptoms in the upper or lower tract or involvement of both is not known. A bronchial ring taken at operation from an asthmatic allergic to grasses will contract when exposed to grass extract.[16]

The presence of the antibody in the circulation does not solely determine the occurrence, the location or the severity of the symptoms. For instance, a patient with a strongly positive ragweed skin test may have no symptoms in the ragweed season. The size of the skin test is a good indication of the dose of injected allergen likely to be tolerated, but it is a relatively poor indication of the severity of the symptoms that may or may not be produced on natural exposure to the allergen.

The patient with the skin sensitizing antibody differs from the artificially sensitive animal or man in that the antibodies may remain at an almost even level for several or many years. It can be concluded that either the normal elimination of the antibody is blocked or that it is continually being formed.

In spite of previous attempts, the characteristic antibody of the allergic

diathesis has been produced only recently by injecting ragweed in a few subjects.[30] This might be expected because when Kuhns[17-20] studied the response to a booster dose of diphtheria toxoid in 131 medical students (at least 10 per cent of whom would be expected to have the allergic diathesis) only two developed the prolonged, even, high level of skin sensitizing antibody characteristic of the disease. This would suggest that attempts to produce this type of response in a small number of persons might readily miss the two in 131 conditioned at the moment of the experiment to give this response.

The Antibody Peculiar to the Allergic Diathesis Has The Following Properties:

1. It produces a characteristic specific local sensitivity to the allergens of the donor when serum containing it is injected into the skin of a normal subject. (Immediate wheal type of reaction).

2. Small amounts of serum may be required for this passive transfer reaction. As little as 0.1 cc of 1/1000 serum dilution may be sufficient.

3. The antibody usually remains at the site of injection in the skin for several weeks.

4. It is non-precipitating, non-agglutinating and behaves as though it were unipolar instead of bipolar.** In other words, it fails to bind together two red cells or two large molecules of protein to form a precipitate or an agglutinate. Because of this apparent loss of a bond, this antibody is sometimes referred to as incomplete antibody. It is also possible that the second bond is present but already in use by a particle too small to cause precipitation when the antibody unites with a single red cell or antigen molecule. In support of this second possibility, the antibody of the allergic diathesis may be slightly larger than the usual bipolar gamma globulin antibodies. It appears to be heavier on ultra centrifugation and fails to cross the placental membrane. There has been considerable confusion both in ultra centrifugation and electrophoretic experiments because the sensitizing substance fails to appear in consistent proportions in the same fractions. Kuhns[21] has been able to take an actively skin sensitizing fraction obtained by electrophoresis and separate it into two parts, neither of which will sensitize skin alone but which regain activity on being mixed.

5. The passive transfer reaction is blocked by specific blocking antibody. This blocking antibody is a bipolar gamma globulin type antibody obtained from patients who have been given injections of the allergen. The blocking effect can be overcome if an excess of allergen is used in testing.

6. The allergic diathesis antibody is readily destroyed by shaking in air.

7. It is readily destroyed by heat (56° for 30 minutes).

**For reasons relevant to its size, there is some question as to whether antibody is multipolar rather than bipolar. However, these substances may not be static, and for practical purposes they behave in reactions as if they were bipolar.

8. To freeze-dry quickly for storage, it must be spread in a very thin layer or else it will be destroyed.

9. It may be destroyed by using copper containing metals which are often used in filters.

10. It may be preserved in the frozen-dry condition or at refrigerator temperatures for a considerable period of time.

THEORETICAL ROLE OF AN INFECTIOUS AGENT

Bacteria: That bacterial infections of the respiratory tract play a part in the exacerbations, remissions and continuation of symptoms is a daily observation in allergy practice. The removal of these infections is an essential part of treatment in both the intrinsic conditions and the extrinsic allergies.

Tuberculosis was recognized as a family disease before it was recognized as a contagious disease. Its epidemiology resembles that of the allergic diathesis, possibly because, like the allergic diathesis, activity of the disease and susceptibility to it varies with age, intercurrent infection, stress and other life factors which encourage transmission among those living in close contact.

Infantile eczema lesions are found to be infected by hemolytic staphylococci or streptococci in some 75 per cent of the cases. However, when routine cultures of the nasopharynx and sputum are made in asthmatic patients, any one or none of the usual respiratory pathogens may be found, even in purulent sputum which clears rapidly when appropriate antibiotics are used. Hemophilus influenzae would appear to be the most frequently found pathogen when special methods are used to detect it.[31]

There are various ways in which infection may modify the immune process. Bacteria or their products sometimes act as adjuvants. Thus, if Burkey's staphylococcal toxin is injected into a rabbit at the same time as ragweed, it requires only a small fraction of the dose of ragweed usually needed to produce sensitization.[23] The use of tubercle bacilli in Freund's adjuvant is another example of enhancement of sensitization by bacteria. Infection may also act as a localizing factor for antibody. For example, when mice are immunized intraperitoneally with influenza virus, the amount of antibody in the bronchial tree can be increased greatly by producing a mild inflammation in the bronchi with any of a wide number of substances or bacteria.[24] This antibody in contradistinction to that of the allergic diathesis, does not remain after the cessation of the inflammatory reaction.

The author cannot make a completely clear picture of the mechanisms by which a single bacterium might produce all the phenomena of the allergic diathesis, nor can this possibility be ruled out.

The Possible Role of a Virus: If a virus is responsible for the allergic diathesis, the characteristics that would make it capable of producing the disease and its peculiar antibody can be more distinctly defined.

The *one* special property that would be required of such a virus would

be the ability to become firmly adsorbed to one pole of normally bipolar antibody (by virtue of the antibodies' properties as a distinctive type of protein rather than its specificity for dust, ragweed, et cetera). Adsorption is a common property of virus. In support of this possibility, the circulating skin sensitizing antibody peculiar to the allergic diathesis behaves as though it might have a small particle blocking one pole (see the properties of allergic diathesis antibody) and must be handled in exactly the same manner as several known viruses.

The natural history of such a virus and its relationship to the disease might be something like this: In early infancy and during breast feeding, the infant would be protected from initial infection by maternal antiviral antibody. When this period of immunity ended, the infant could become infected on the skin or in the membranes of the respiratory tract. Like *herpes simplex,* this might well be encouraged by other bacterial or viral respiratory infection.

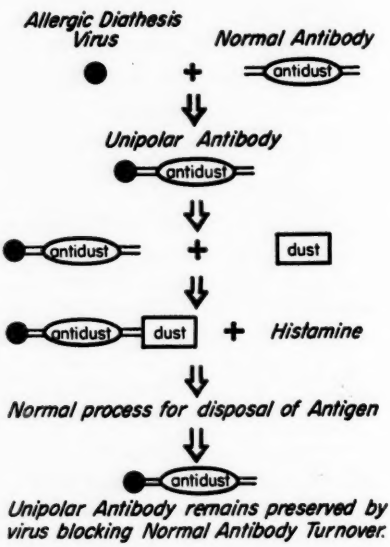

Fig. 2. Mechanism by which a unipolar antibody might be formed.

In the lesions the virus would multiply and attach itself to receptors in the epithelium and to whatever suitable antibodies were available at the time. In young infants exposed for the first time to many foods, the latter are often antifood antibodies and a little later, particularly when the lesion is in the respiratory tract, the most common antibodies available would be those to the inhalants.

The accompanying diagram describes the mechanism by which such a unipolar antibody might be formed.

The localization of the symptoms of the allergic diathesis (which has never been satisfactorily explained) could depend upon the location of the virus in the cells of the nasal membranes, the bronchial tree or the skin. The virus would be activated, and unipolar antibody would be formed chiefly at the times of other respiratory infection (as evidenced by proliferative changes characteristic of virus stimulation). Exposure to allergens to which unipolar antibody had previously been formed could produce symptoms with little virus activation and multiplication. (Relatively little proliferative change in the membranes is produced by allergic reaction in the absence of bacterial infection or other apparently non-specific irritants). On the other hand, when bacterial or other respiratory infection occurred, the activation of the virus might produce symptoms in the presence of relatively little allergen. When bronchial infection, such as influenza, whooping cough, measles, bacterial bronchitis or accidental exposure to an irritating gas occurred during a time of virus activity in the nose, the virus could spread to the damaged membranes of the lower tract and asthma would begin.

As with *herpes simplex,* the infant and the young child may be most likely to begin symptomatic disease, but also as in *herpes,* many individuals who have never had symptoms of the disease may have antibodies to the virus in adult life. In the adult, initial infections occur more often in people who have moved from areas where the disease is less common or in those who have not developed immunity from early family contact with the disease. In older people, the pattern tends to change, and skin fixed or circulating unipolar antibody is much less common (perhaps because the antiviral antibodies of the blood may reach levels that no longer allow the virus to circulate).

At this stage, sinus and bronchial infections appear to play a major role, and proliferative changes in the swollen nasal membranes and hypertrophic sinusitis become prominent features. Proliferation and necrosis are characteristic of many virus lesions. This pattern, although it is the usual one in late life, may appear much earlier in any situation where excessive activation of virus by recurrent or chronic bacterial infection has taken place. This activity may call forth antibody production to the point of destroying circulating virus without killing the inaccessible virus in the mucosal cells or skin. (Thus the inverse relationship to proliferation at any age). In seasonal allergies, for example ragweed hay fever, if there is no increase of virus activity by intercurrent infection during the ragweed season, hay fever symptoms may disappear over a period of years as the amounts of unipolar antibody gradually decrease. If there are relatively few virus particles in the membranes, they may occasionally die out completely. As a rule they merely remain quiescent to manifest themselves again sometimes years later when infection or stress reactivates the disease. From time to time, other sensitivities may appear depending on the nature of the allergens present at the times of respiratory-infection-produced exacerba-

tions. In the older patient, when chronic bacterial respiratory infection becomes entrenched, the intrinsic picture of recurrent viral activity may develop.

This picture is *only a hypothesis* binding together a large collection of clinical and laboratory observations. The author hopes, however, that it serves to point out that an inherited tendency to produce abnormal antibody is by no means the only possible explanation of the allergic diathesis.

The controversial subject of psychogenesis in allergy has not been considered because, like heredity, psychophysiological stress has been shown to play a part in at least some bacterial and viral infections. (Tuberculosis and *herpes simplex,* for example). The observation that psychological factors, particularly major catastrophies, may sometimes coincide with the onset of symptoms in this disease in no way argues against the hypothesis presented here.

In summary, many characteristics of this disease suggest phenomena familiar in infection, particularly viral infection. Some of these are:

Neonatal immunity
Transmissibility (proven at least within the family)
Greatest susceptibility in the infant and young child
Increased susceptibility in pregnancy
Differing incidence in rural and urban areas
Increased incidence in a new community } 65 to 80 per cent of these cases occurring in those who have no previous history of the disease in themselves or their family
Increased incidence in new immigrants }
Changing pattern with age
Variation of activity
Activation by intercurrent infection
Proliferative and necrotizing lesions
Specific localization of lesions
A possible effect of immune serum
Variation in pathogenicity and affinity for specific locations

An epidemiological study such as the one begun here can only hope to add another reason for looking further. In failing to consider the possibility of infection in this disease, we may have been missing an opportunity towards its eventual control. We may also have been missing a chance to gain new understanding of the interplay between the phenomena of allergy and those of infectious disease so evidently important in the pathology of many other disorders.

SUMMARY

A study of 432 patients with the allergic diathetic disease shows a very high rate of close contact with the disease among patients who do not have a positive family history of allergy. A pattern of incidence compatible with infection where the family history is positive is also obvious. The disease is described and possible mechanisms are discussed.

The data in this paper are not suggested as proof that the allergic diathesis is caused by an infectious disease but is given as reason to consider this possibility.

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PROPHYLACTIC TREATMENT OF MIGRAINE HEADACHE AND HISTAMINE CEPHALALGIA WITH A SEROTONIN ANTAGONIST (METHYSERGIDE)

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THE TREATMENT of migraine headaches undoubtedly has been a matter of concern since the earliest days of antiquity when Arateas of the ancient kingdom of Cappadocia first described it as "heterkrania." Later, the renowned Greek physician, Galen, renamed the headache, migraine. It is by that name that the syndrome is known today. From those early days to the present time, every endeavor has been made to render relief from the severe headache and its associated symptoms. The prevention of its periodic recurrence has been the ultimate aim. These efforts received the greatest productive impetus when the vascular origin of migraine and the action of ergotamine tartrate was reported by Graham and Wolff in 1938.[1]

Ergotamine tartrate, either alone or in combination with caffeine, still remains the most effective drug today to abort a migraine attack. It is recognized that the earlier the drug is used after the onset of the attack, the more effective it is in shortening the duration of the headache and relieving the pain. The beneficial effect of ergotamine in providing relief is generally attributed to its vasoconstricting property on the extracranial branches of the external carotid artery. However, within the last few years it has been shown that ergotamine tartrate may possess in addition, some antiserotonin activity.[2,3]

In 1957, Ostfeld and his workers[4] demonstrated that vasodilatation was not the sole cause of the migraine headache, but that accompanying the vasodilatation was the local presence of a substance or substances such as serotonin, histamine, and neurokinin which were capable of lowering the pain threshold. Wolff and his associates[5] were able to demonstrate that temporal perivascularly-injected serotonin produces symptoms similar to those observed in migraine. It was thus speculated that serotonin might be involved in the acute pain sensitivity experienced by migraine patients during an attack. Furthermore, because serotonin is suspected of playing a role in various forms of allergic diseases,[6] and migraine is sometimes ascribed to an allergic reaction, it was thought that serotonin might be implicated in the production of the headache, itself. It was therefore decided to employ a potent serotonin antagonist between attacks to ascertain its effect, if any, in preventing subsequent seizures. If the attacks

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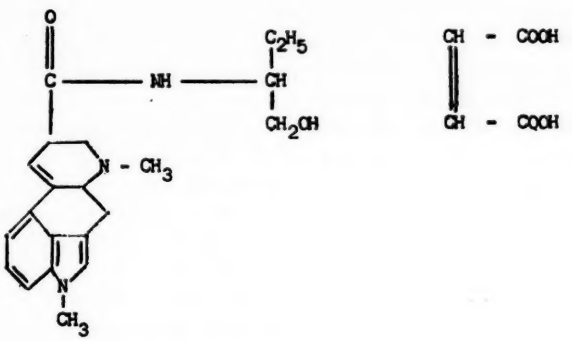
still persisted, the influence, if any, of the antagonist on the pain associated with an attack would be observed.

The drug chosen for this study was Methysergide® (methyl-lysergic acid butanolamide)* because Doepfner and Cerletti,[3] in a study of the



$C_{21}H_{27}O_2N_3$ $C_4H_4O_4$

Fig. 1. Formula for Methysergide.

derivatives of d-lysergic acid for antiserotonin activity, had found that this agent possessed the greatest antiserotonin potency. An additional reason for choosing this drug was that it has a feeble adrenergic action and, in animals, does not exert any direct action on the peripheral circulation, indicating little or no vasoconstricting property. Its physiologic effect, therefore, would be due entirely to serotonin neutralization. It also is relatively harmless in humans in doses up to 5 mg intravenously.[7] The formula of this chemical is shown in Figure 1.

PROCEDURE

Fifty patients were selected for this study, of whom forty-five had an established diagnosis of migraine and five were afflicted with histamine cephalalgia. The youngest patient was twenty-eight years of age and the oldest, fifty-five. In the migraine group, there were fifteen men and thirty women. In the group who suffered from histamine cephalalgia, there were three men and two women. Thorough medical, neurologic, endocrine, roentgenographic, and allergy studies were done on the patients to exclude all physiologic, biochemical, or electrolytic disturbances which theoretically might conceivably be a cause of the headache. No patients whose difficulty might indicate a specific allergen as an etiologic factor were accepted for this investigation. None of these patients suffered from vitamin

*Kindly furnished by Mr. Harry Althouse of Sandoz Pharmaceuticals.

deficiencies, hypoglycemia, or any demonstrable ocular malformation. There was no history of trauma to the head and neck in any of the patients in this group; neither were there any who showed any signs of so-called "gastrointestinal intoxication." The frequency of their attacks varied from once or twice a week to daily attacks; the duration from several hours to several days. They gave a history of having suffered from migraine from three and one-half years to "as long as I can remember." All had used the routine preparations for the relief of their headaches including ergotamine tartrate in one form or another.

At the beginning of this study, 2 mg tablets of Methysergide were prescribed every four hours. Because several patients on this dosage schedule experienced nausea and vomiting, the dose was reduced to 2 mg, three times a day after meals. A few patients who still complained of nausea were given an anti-emetic, orally, to be taken at the same time as Methysergide. The anti-emetic used was one under investigation by us, thioethyl-3-[(methyl-4″-piperazinyl)-3′-propyl]-10 phenothiazine dimaleinate, Torecan®-Sandoz. Despite this combination and a further reduction in dose, four patients had to discontinue the medication because of nausea, vomiting and a "sick feeling." Two other patients complained of vertigo regardless of dose and refused to continue the medication. One patient reported spasm of the neck muscles and two, of the calf muscles; but these untoward symptoms, for which we could ascertain no cause, wore off as the treatment was continued.

After the Methysergide tablets (three times a day) had been taken for three days, the dose was finally reduced to one tablet (2 mg) morning and night. This dose, with the exception of two patients who, without our knowledge at the time, reduced the dose to one tablet daily, was continued for six months.

RESULTS

As indicated, six of the migraine patients discontinued taking the drug for what may be assumed to have been untoward side effects, namely, nausea, vomiting, vertigo, a "sick feeling" or "lightness in the head." Of the thirty-nine patients remaining, thirty reported excellent results; that is to say, they were entirely relieved of their headaches and had no recurrences. Five reported that although they continued to have headaches, they were sporadic, did not last long and were of no serious consequence. This may well be considered a good result. Four patients had no relief whatsoever from the tablets. Their headaches came just as often, lasted just as long, and were just as severe as formerly.

In the five cases of histamine cephalalgia, which is sometimes described as a migraine variant "cluster" headache, the results were nothing short of dramatic. This type of headache is probably the most annoying of head pains. It is associated with vasodilatation, engorgement of the temporal vessels, plugged nasal passages, lachrymation, rhinorrhea, flushing of the side of the face and an increase in the surface temperature over

the eyebrow in the frontal area. All of these five patients responded effectively to Methysergide and have had no attacks of histamine cephalalgia since taking the drug. There was no evidence of any physical change in any of the patients while being studied; blood pressure and pulse rate values remained constant.

At the beginning of this investigation, a double-blind study using placebos was not initiated. In the middle of the study, however, placebos which had the same physical appearance as the active tablets were employed for eight consecutive weeks in sixteen of the migraine patients who had previously received relief with Methysergide. Neither the investigator nor the patient was aware of the substitution of the placebo for the drug. This was deemed necessary to exclude psychological factors on the part of the patients, as well as the possibility of bias on the part of the investigator.

In this group, four of the patients continued to be relieved with the placebo for an additional three weeks, although they all remarked that the medicine seemed to be losing its efficacy. They still felt that they were improved, but their headaches seemed to be returning—although not with the same force as before. At the end of the third week, all four reported that their headaches were just as bad as ever. One additional migraine patient during the sixth and seventh week thought that the drug which had not seemed to be doing her any good was now once again becoming effective. However, on the eighth week, she was quite disgusted and exclaimed that her sick headaches were no better than when she first started using the tablets.

Tests by Udenfriend and his co-workers[8,9] to determine the amount of serotonin in the blood and the breakdown product, 5-Hydroindoleacetic acid, in the urine—have been devised and are routinely used in the diagnosis of carcinoid tumors of the intestine, called argentaffinomas. We used these tests but did not find them to be of any value in migraine. The metabolite, 5-Hydroxyindoleacetic acid, was not found in excess either between or during acute attacks.

Although it would appear that the excellent results herewith reported were due entirely to serotonin neutralization (and others have reported similar results[10-13]), on the basis of current knowledge and pharmacologic evidence, it cannot be stated with assurance that each and every migraine headache is associated with the liberation of serotonin; nor can one unequivocally state that the local presence of serotonin is solely responsible for the lowering of the pain threshold and the consequent experience of head pain.

SUMMARY

Forty-five patients with migraine and five with histamine cephalalgia were treated prophylactically with a serotonin antagonist (Methysergide). Side effects after the first few doses consisted of nausea, vomiting, a "sick feeling," vertigo, "lightness in the head," and muscle spasm. An antiemetic tablet administered with the Methysergide tablet relieved all but

four of those who complained of nausea or vomiting. Two patients, complaining of vertigo, refused to continue the medication. The other side effects disappeared within a few days. Blood pressure and pulse rate values remained constant.

Thirty of the remaining thirty-nine migraine patients reported no subsequent headaches after taking the drug. Five reported sporadic minor headaches. Four reported no relief. All five of the patients with histamine cephalalgia reported complete relief from attacks while taking the drug.

A double-blind study using placebos was performed for eight consecutive weeks on sixteen patients who previously had been relieved of their headaches. Four of these patients thought they were still obtaining relief for the first three weeks but reported that "the drug seemed to be losing its efficiency" during the subsequent five. One patient during the seventh week thought she obtained some relief that week, but on the eighth week was convinced that the "drug" was of no value.

As a result of this study, it is postulated that serotonin may be an important factor in the production and continuance of the migraine syndrome, and in histamine cephalalgia. A potent serotonin antagonist appears to be an effective and well-tolerated agent for reducing the severity and frequency of attacks.

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EVALUATION OF THE REPOSITORY EMULSION TREATMENT OF RAGWEED POLLINOSIS

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IN THE PAST several years, there has been an increasing interest in treating allergic respiratory disease by means of the repository form of injection. Many allergists are interested in using this form of treatment, but they continue to be skeptical because of the following factors: the potential hazards involved, the supposed difficulties encountered in making the emulsion, the uncertain patient-acceptance of this innovation, and the divergent results that have been reported by various allergists and groups using this type of treatment. We undertook this project to find out how effective the treatment was in our hands and how it compared with our routine standard treatment.

METHODS

We used a modified Loveless[1] technique for making our emulsion. We mixed 3 cc of Atreol and 2 cc of Falba. This mixture was then sterilized in a Dri-clave at 225° F for one hour and stored in a refrigerator until used. To this mixture we added varying strengths of our ragweed solution extracted in Coca's alkaline fluid. This extract was standardized in two separate laboratories by utilizing the method of Cooke and Stull for determining the protein nitrogen. The Atreol, Falba and ragweed extract were drawn into a 10 cc Luerlock syringe. This syringe was attached to a three-way stopcock with a similar empty syringe attached at right angles. The opening of the stopcock was then adjusted so that sixteen complete strokes per minute would occur. A complete stroke consists of the passage of the mixture from the loaded syringe into the empty syringe and then back into the original syringe. Seven minutes was required to produce an homogeneous thick emulsion. Each new emulsion was checked by means of microscopic and water droplet inspection and by skin prick test with a control of our concentrated ragweed extract on a known ragweed sensitive individual.

Since this was our first venture into this field, we decided to give to most all of our patients two injections. Five patients received only one pre-seasonal injection of ragweed emulsion. Therefore in Table I there are 183 patients who received the one injection and only 178 patients who received a second injection.

Table I summarizes the number of patients who received first and second injections during the periods specified.

CHOICE OF PATIENTS

The group totaled 183 patients. All patients were from our own practice, and only those who had good follow-up studies and evaluation during the

ragweed season were included. Routine hyposensitization treatment had been received by 170 patients during previous years. This treatment consisted of weekly injections of ragweed extract given either on a perennial or a pre-seasonal basis. Of this group, 165 had not received any injections

TABLE I. DATES OF FIRST AND SECOND INJECTIONS

First Injection	Second Injection
May 1-31 36 patients	June 1-30 5 patients
June 1-15 54 patients	July 1-10 1 patient
June 16-30 79 patients	July 11-30 41 patients
July 1-15 13 patients	July 21-31 104 patients
August 1-15 1 patient	August 1-15 27 patients

TABLE II. SEX DISTRIBUTION

Male	Female
98	85

since September or October of the previous year. Five patients had ceased treatment at different times during the year because of their desire to take the emulsion form of therapy. Another group of thirteen cases included new patients who had never received any injections of ragweed extract. The large group of previously-treated patients was weighted with so-called "failures" or poor results utilizing our routine ragweed hyposensitization methods. The previously-treated group also included many highly sensitive patients who could not tolerate high doses of aqueous ragweed extract because of local or generalized systemic reactions.

TABLE III. AGE DISTRIBUTION

Age in Years	0-5	6-10	11-20	21-30	31-40	41-50	51-60	61-70
Number of Patients	4	30	64	13	33	26	10	3

Tables II and III give a breakdown of the entire group of patients according to sex and age distribution. The youngest child treated was four years of age.

RESULTS

We have classified our results as follows:

1. The "excellent" group included those patients who had either no complaints or minor complaints requiring no medication.

2. The "good" group included those patients having minimal symptoms for several days, usually during the height of the season and requiring antihistaminic agents.

3. The "fair" group included patients who had symptoms for one week or longer and required antihistaminics.

4. The "poor" group included patients who had relatively no relief from the emulsion injections and required antihistaminic agents and often corticosteroid hormones for relief of their allergic symptoms.

Table IV shows the number of cases in each classification and the percentage of the total that each group comprised.

TABLE IV. RESULTS OF 183 PATIENTS TREATED WITH REPOSITORY EMULSION

	Excellent	Good	Fair	Poor
Number of Patients	62	65	28	28
Percentage of Total	(33)	(36	(15.5)	(15.5)

We determined the total dose expressed in protein nitrogen units that each patient received. There did not appear to be any correlation between the total dose and clinical results. Total individual doses ranged between 7,000 PNU to 21,000 PNU. The average dose given to individuals of the excellent and poor groups was 17,000 PNU while those in the good and fair groups had average doses of 16,000 PNU.

REACTIONS

Systemic reactions even in highly sensitive patients were infrequent and of no clinical significance. Two patients, one of whom complained of nasal stuffiness and the other of vague "tightness in the chest," were considered to have suggestive symptoms of a systemic reaction. Neither medication nor emergency therapy was required. Nine patients who had received their first ragweed emulsion injection experienced large local reactions lasting three days to several weeks. Only one patient developed a local reaction with the second emulsion injection. This individual had also had a local reaction with the first injection.

Two documented sterile abscesses were seen. Both abscesses were aspirated and cultured. No organisms grew on the culture media. Both abscesses required incision and drainage.

One of these patients, a forty-five-year-old woman, received her ragweed injection in June 1960. She returned in early August and complained of a sore swollen arm. The area was warm, tender and fluctuant. After conservative therapy including heat and antibiotic agents, the mass was aspirated. The material appeared serosanguinous with a thick white milky substance floating at the surface.

The second patient, a forty-five-year-old man, received one injection on August 5, 1960. There was an excellent result with minimal symptoms. On September 13, he noticed a sore lump on the upper arm. On September 16, 1960, the area was fluctuant, warm and tender. He was tried on oral

steroids and antibiotic agents for one week without any appreciable regression of the mass. Aspiration revealed purulent-looking material but the culture was negative. No organisms were seen on a stained smear of the material. Surgical incision and drainage of the abscess was also necessary in this case.

TABLE V. COMPARISON OF STANDARD AND REPOSITORY TREATMENT METHODS

	Excellent		Good		Fair		Poor	
	Stand.	Rep.	Stand.	Rep.	Stand.	Rep.	Stand.	Rep.
Number of Patients	25	62	51	65	12	28	12	28
Percentage of Total	(25)	(33)	(51)	(36)	(12)	(15.5)	(12)	(15.5)

* "Stand." refers to the standard hyposensitization cases while "Rep." refers to the emulsion repository cases

DISCUSSION

Before reviewing other authors' results and comparing them with ours, it would be of interest to compare the results of a *comparable* group of ragweed hayfever patients whom we treated during the 1960 season in the routine standard method. Table V shows these comparisons. "Stand." refers to the standard hyposensitization cases while "Rep." refers to the emulsion repository cases.

We went through our files and collected consecutively the first 100 patients who had received routine ragweed pollen injections for the 1960 ragweed pollen season. This group included a mixture of both the perennial and pre-seasonal forms of treatment. The figures in Table V compare the results and the percentage of each classification. In the standard treatment group, the excellent and good cases comprised 76 per cent of the total, while similar groups under repository treatment totaled 69 per cent of the entire series. These figures indicate that the two types of treatment gave reasonably similar results.

We have compiled five other series of ragweed hayfever cases treated with the repository emulsion injections. These include Brown's 1957, 1958 and 1959 series, Furstenberg's 1959 composite series and Feinberg's small series of twenty-four cases. The results are tabulated in Table VI.

If we collect all the good and excellent cases into one group and the fair and poor cases into a second group, the results of Brown's 1957 series, Furstenberg's 1959 group, Feinberg's twenty-four cases and our series, are remarkably similar. The percentage of the total of excellent-good cases is 74 per cent, 73 per cent, 70 per cent and 69 per cent respectively.

So far, we have dealt with hard, cold inflexible facts and statistics. We believe that it is important at this time, to discuss some of the warm, intimate and vital factors which bear heavily on the outcome of such a study. Unfortunately, these are the intangibles of clinical, practical medicine and are not subject to biopsy, analysis and critical evaluation. The evaluation and classification of results have always posed a problem

in clinical allergy. It is important to see and observe each patient during the pollen season so that the complaints may be recorded at the time they occur. The retrospective method of evaluating pollen seasons by sending cards is, in our opinion, not an accurate or true reflection of the facts. There are many patients who complain for three or four days

TABLE VI. COMPARISON WITH FIVE OTHER SERIES OF PATIENTS

Group	Excellent	Good	Fair	Poor
Brown, E. A.[3] 1957 38 Patients	28 near-perfect (74)**		6* (14)	4* (12)
Brown, E. A.[2] 1958 685 patients	perfect (84)	113 failures—any symptoms (16)		
Brown, E. A.[4] 1959 1064 patients	perfect (87)	144 patients (13)		
Furstenberg[5] et al 1959 1036 patients	762 patients (73)		274 patients (27)	
Feinberg[6] 24 patients	4 (16)	13 (54)	2 (8)	5 (22)
Fine and Abram 1960 183 patients	62 (33)	65 (36)	28 (15.5)	28 (15.5)

*Our interpretation of the chart from the original article.
**Numbers placed in parentheses indicate per cent.

during the season but who, when asked in December, will rave about what a wonderful season they had in August and September. It is important to treat the patient pre-seasonally and follow up the treatment with "co-seasonal" observation.

Another factor of importance which influences this type of evaluation is the patient-doctor rapport. Many patients "want to please" the doctor and will minimize their complaints. Unfortunately, objective signs of a pale boggy mucosa do not always correlate with subjective symptoms, and the inverse situation is also true.

We have had reason to suspect that the financial cost of hyposensitization influenced the degree and frequency of complaints. Several patients who did well on minimal pre-seasonal aqueous treatment at a relatively small cost, had seasonal symptoms when given emulsion injections. Some of these patients complained about the cost of the "new shots" and expressed a desire to take the regular injections next year.

Even though the over-all results between the two forms of treatment appear to be similar, the advantages of this new form of therapy leads us to think that it will be a useful tool in the allergist's armamentarium. The reduction in frequency and total number of office visits appeals to both the patient and the doctor. It reduced the inconvenience of weekly injections to which many patients objected. It was acceptable to many children who balked at taking the multiple-dose injections. It reduced the patient traffic-load in our office to a point where each patient could receive a little more time and personal attention.

One of the unsolved problems remaining is: Of those patients who did

well, *which ones would have done well without any therapy at all?* It is known and accepted that many patients treated for several years can have symptom-free seasons without further injections, at least temporarily. In our private practice, we did not deem it proper to try placebo injections with this group of patients. Table VII shows the group of excellent responses and how they compared with the previous year's therapy.

TABLE VII. EVALUATION OF EXCELLENT GROUP

Better	Same
35	27

The group of twenty-seven patients who stated that their symptoms were the same as last year, conceivably would have done well without any treatment. Because of the patients' desire for treatment and because of the uncertain, unpredictable nature of clinical allergic problems, they were treated this past ragweed season with the repository emulsion form of injection.

SUMMARY

The treatment of ragweed pollinosis by both the standard and the repository emulsion method appears to be equal in effectiveness.

There appears to be no relationship between the reported results and the total amount of antigen injected.

The advantages of the repository form of treatment, as outlined in the discussion, make it a valuable adjuvant to our present forms of therapy.

The hazards and problems of evaluating results in allergic patients are discussed.

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THE SCOPE AND CHALLENGE OF THE FIELD OF HYPERSENSITIVITY

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TO MANY PATIENTS and even medical colleagues, the term "allergy" has indicated, in a restrictive sense, a variety of ailments like asthma, hay fever and eczema, the therapeutic resolution of which is dependent on the astute application of skin tests, elimination diets, and injections for desensitization. It might properly be added parenthetically that the inordinate use of these procedures, to the exclusion of careful appraisal of the needs of the patient as a whole, has in some instances put our specialty in unfavorable perspective in the eyes of laymen in general and of physicians in other branches of the healing art.

In recent years the impact of basic research in the field of immunology has been tremendous. The development of many new tools, technics and devices for study in this area has changed completely the formerly held narrow concept of allergy. The new methods of investigation thus made possible have demonstrated that mechanisms of hypersensitivity are involved in many clinical problems.

Allergy, or the field of hypersensitivity, is attaining maturity and medical stature, and is impinging more and more on many of the well-established specialty disciplines. New frontiers in allergy have been opened by the laboratory studies mentioned. These have broadened greatly the scope of allergy and the responsibility of the physician who devotes his major time to problems in this field.

It is pertinent, and I believe of general interest, to take up more in detail some of the currently popular areas of investigation in which an accumulating body of evidence indicates that immunologic factors play a major role. In this way it will be possible to illustrate by specific example and thus substantiate some of the generalizations which have just been made.

AUTO-IMMUNE DISEASE

One of these areas is that of the auto-immune diseases. The basic mechanism leading to the development of such a disorder has been postulated to be alteration in the composition of normal body protein, thus rendering it antigenic. Factors causing this change may be invasion of cells by bacteria or viruses or union of cells with drugs, thus forming protein conjugates which lead to the formation of auto-antibodies.[2] Examples of a number

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of clinical conditions in which auto-immune reactions are operative will be cited briefly.

The sequence of events in the development of endophthalmitis phaco-anaphylactica probably is as follows: Some of the lens protein, ordinarily inaccessible, escapes into the anterior chamber at the time of extraction of the cataract. This, possibly in the presence of staphylococci or other microorganisms which act as adjuvants, leads to the formation of auto-antibodies which in turn produce the local reaction characteristic of the disease. Burkey was able to sensitize rabbits to lens protein by injecting the animals with this material together with staphylococci. Thereafter, if the lens were needled and protein thus released from it, the animal would develop endophthalmitis phaco-anaphylactica.

Much evidence has accumulated to suggest that multiple sclerosis and encephalomyelitis may have an auto-immune basis. The development of these disorders may occur following the use of antirabies vaccine which contains some spinal cord tissue. This fact supports this concept. Also, syndromes associated with demyelinization frequently follow infectious diseases, suggesting that the microorganisms may act as adjuvants and set the stage for the development of auto-antibodies.[2]

In laboratory animals, lesions resembling those of multiple sclerosis have been produced repeatedly by injecting emulsions of homologous brain or spinal cord with Freund's adjuvant. In January, 1960, Paterson[14] reported the production of allergic encephalomyelitis in rats by this method. In most ingenious experiments, he was able to transfer this condition by sensitized cells to other rats previously rendered immunologically tolerant, thus suggesting that the disease is mediated by the mechanism of delayed hypersensitivity.

For some years, systemic lupus erythematosus has been considered to be of auto-immune origin. The serum of patients afflicted with it contains an abnormal gamma-globulin which will react with white blood cells *in vitro* to produce lupus erythematosus cells. Rabbits immunized with this gamma-globulin develop specific antibodies against it which, when mixed with lupus erythematosus serum, will prevent the production of lupus erythematosus cells *in vitro,* as just described. Studies have shown that the lupus erythematosus factor behaves like an auto-antibody to all nuclei and to desoxyribonucleic acid (DNA). The administration of drugs like hydralazine (apresoline) and penicillin has led to sensitization in some patients and thus has triggered the auto-immune mechanism, bringing about the development of the picture of systemic lupus erythematosus.[7]

The demonstration of the rheumatoid factor in the serum of patients afflicted with rheumatoid arthritis has heightened speculation as to the auto-immune nature of this disease. Studies with the ultracentrifuge and by electrophoresis suggest that this factor is a gamma-globulin of the 19S type. The present hypothesis[12] is that it reacts with some component of

gamma-globulin but that in normal serum there is an inhibitor to this reaction. The antigenic material is thought to be DNA protein, altered possibly by streptococcal disease, thereby becoming antigenic. By the fluorescent dye technic, globulin of patients with rheumatoid arthritis has been shown to combine with nuclear material of tissue cells. Available evidence indicates that the rheumatoid factor has features of an auto-antibody.

The concept of a possible auto-immune mechanism in some purpuras may have been motivated by studies done in 1921 by Bedson. He showed that in guinea pigs the platelet counts could be greatly reduced by the injection, intraperitoneally, of a rabbit antiserum for guinea pig platelets. Also damaged in these same animals was the vascular endothelium.

Purpura as a manifestation of sensitivity to allylisopropylacetylurea (sedormid) has been observed. It seems likely that the drug forms a sedormid-platelet conjugate which becomes antigenic to the patient. The serum of such an individual will lyse platelets *in vitro* only in the presence of sedormid; a patch test with the drug on the unbroken skin will elicit a purpuric lesion.[7]

The plasma of patients with idiopathic thrombocytopenic purpura will lyse platelets from a normal or a purpuric individual. It will also lower the platelet count of rabbits. Harrington and his associates injected blood plasma from patients with idiopathic thrombocytopenic purpura into normal healthy persons with consequent marked lowering of the platelet count in the latter. What causes patients with this type of purpura to develop antibodies to their own platelets is not established, but it would seem to be a type of auto-immune response.[2]

The development of thyroiditis is thought to be contingent on an auto-immune mechanism. The antigenic material here is thyroglobulin, and at times cytoplasmic protein; it is of the inaccessible type. What process leads to its egress from the thyroid acini and its subsequent alteration so that it becomes antigenic is not definitely known. Precipitating and nonprecipitating antibodies have been demonstrated in the serum of patients with thyroiditis.[16]

A disease closely resembling acute glomerulonephritis in man has been produced in rabbits by Masugi.[13] This was accomplished by sensitizing ducks to an emulsion of rabbit kidney. Thereafter the antirabbit-kidney duck serum was injected intravenously into rabbits with the development of the disease five to seven days later. In man, acute glomerulonephritis is known to come on seven to fifteen days after an acute upper respiratory infection, especially the type caused by group A hemolytic streptococci. It has been theorized that the microorganisms in some way lead to the formation of auto-antibodies that localize in the renal glomeruli. It is known that a reinfection will cause an exacerbation of the glomerulonephritis within two to three days—the so-called anamnestic response.[15]

In concluding this brief consideration of illustrative auto-immune diseases, I should emphasize the diversity of bodily tissues affected by them and observe that our recognition of their presumed immunologic basis has not solved the therapeutic problems which they pose.

TISSUE TRANSPLANTATION

Another major area of research in which mechanisms of hypersensitivity play a dominant role is that of tissue transplantation. Problems with challenging interest from the standpoint of theoretical implications have been raised by studies in this field. In an effort to resolve some of these, Burnet evolved his clonal selective theory of antibody formation for which, with Medawar who contributed so much on immunologic tolerance and tissue transplantation, he shared the 1960 Nobel prize in medicine and physiology.

Most available evidence indicates that the homograft-rejection reaction is mediated by the mechanism of delayed hypersensitivity. Tissue transplanted from one individual to another of the same species sloughs off in ten to fourteen days. It is recognized by the host as "not self" and thus becomes antigenic and is destroyed by antibodies generated by the host.

If the recipient animal and the donor have the same or almost identical tissue antigens, as would be the case in homozygous twins or highly inbred strains respectively, then the graft is accepted and not rejected. The same applies when tissue is taken from one site and applied to another in the same animal. Such tissue is known as an autograft.

Problems of clinical medicine that relate directly to the observations so far described are those in which, first, the grafting of skin for extensive burns is needed, second, the transfusions of marrow cells is warranted because of damage by radiation or disease and, third, the transplantation of an organ is needed. An example is a kidney replacement for a patient whose kidneys have been destroyed. The successful resolution of such instances depends on the development of clinically acceptable technics for making any individual immunologically tolerant of another. In this regard the transplantation of a kidney from one homozygous twin to the other poses no difficulty.

Burnet[5] has observed that acquired immunologic tolerance means simply that the content of "self" components in the recipient animal has been enlarged by experimental manipulation. For example, homologous, potentially antigenic tissue injected into a fetus will come to be recognized and accepted as self by the lymphocyte. Thereby, a state of nonreactivity to, or immunologic tolerance for, the tissue of the donor is produced and when the inoculated animal reaches adult life, it will accept grafts from the donor of the homologous tissue.

Homografts applied to patients afflicted with agammaglobulinemia, lymphoma or sarcoidosis have been reported to be accepted and not rejected as normally would be expected. This suggests that in these natur-

ally occurring conditions the usual immunologic mechanisms are disordered or nonoperative. It also is of interest that in four out of nine uremic patients, renal transplants survived for periods ranging from five to twenty-five weeks.[8] Prolonged survival of skin homografts in uremic individuals has also been observed. The low level of properdin in the blood of these patients may explain their altered immune response.

If the antibody-producing cells—lymphoid, plasma and mononuclear—of a laboratory animal are destroyed by radiation, nitrogen mustard, cortisone or pretreatment with an antiserum, then a homograft will be accepted. In man where the problem has been to graft a kidney or marrow, devices have been employed which it was hoped would cause a temporary cessation of the usually operative immune responses, thus giving the graft a chance to establish itself. Such technics have included total-body irradiation[9] and the administration of 6-mercaptopurine, an agent that may attack directly the antibody-forming tissue.[17] Burnet[4] expressed the opinion that if means can be discovered to maintain a graft for a certain critical period, eventual permanence may be obtained even in the presence of histo-incompatibility between graft and host.

Ferrebee and Thomas[10] reviewed some of the problems associated with attempted transplants of marrow in laboratory animals and man. After total-body irradiation, the antibody-producing cells theoretically should be largely destroyed. Thereafter the intravenous administration of fetal hematopoietic tissue is suggested. Since the host now is immunologically unresponsive and the donor immunologically immature, all should go well. This, in fact, has been the case with rodents. Repopulation of both marrow and lymph organs was brisk and permanent. However, in dogs the transplants of fetal marrow were unsuccessful.

Ferrebee and Merrill[9] have encouraged more trials of marrow transplants in patients afflicted with leukemia. Reported experience,[10] however, indicates that infusions of fetal hematopoietic tissue in man have not led to regeneration of marrow.

The scope of possible research suggested by this brief review of some of the work being carried on in tissue transplantation and the interrelated area of immunologic tolerance is tremendous. Continued investigation in these fields, it is hoped, will solve some of the knotty problems relating to grafting of organs in man.

DEVELOPMENT OF AND RESISTANCE TO CANCER

A third major area of study in which immunologic factors likely play a role is in the development of and resistance to cancer. Homografts of malignant tumors are rejected and undergo second set reactions, as do those of healthy tissue. They are accepted under normal conditions only by members genetically identical to, or highly inbred from, the strain from which the graft has come.

In enunciating his clonal selective theory of antibody formation, Burnet[6] noted that throughout life as many as 1,000,000 body cells each day may undergo mutation. The most serious consequence of such somatic alteration would be the development of a malignant disease. Cytoplasmic homeostasis may be disturbed, with consequent change in self-identity markers, by entrance of a virus into the cell or by exposure to radiation.

Those mutants differing most histologically from the host's tissues are contained and destroyed by the immunologic defense mechanisms of the body. Only those very similar to the host's cells would have a chance to develop into a tumor because the immune response against such cells would be very weak. This in turn would be true because their self-identity markers would be so similar to the host's that they would not be recognized as foreign and thus would not be antigenic.

From a clinical perspective, factors of host resistance seem associated closely with the inception and course of malignant disease in man. The spontaneous regression of established tumors, the prolonged survival of some patients after incomplete removal of their cancers and, finally, the sudden appearance of widespread metastatic lesions many years after successful treatment of the primary lesion all suggest strong power of restraint by the immunologic mechanisms of the patient.

Antigenic material present in malignant tumors has been shown by gel-diffusion technics and passive anaphylaxis to differ somewhat from that obtained from normal tissue. The fact that gamma-globulins are increased in moderately advanced malignant disease suggests an immune mechanism in resistance to cancer. Their tendency to decrease as the disease progresses to preterminal stage suggests a breakdown of this mechanism. The blood level of properdin, a protein having to do with immune reactions, also is decreased in patients with far-advanced malignant disease.

Experimentally induced immunologic tolerance will permit malignant cells to grow in animals that otherwise would be able to reject them by the homograft reaction. Malignant disease often occurs in members of the same family through several generations. The explanation may be that the offspring inherit parental malignancy genes and that these genes render the descendants immunologically tolerant to cancer cells so that the latter are not subject to the homograft-rejection reaction, that is, to containment and destruction.

It is reasonable to hope that continuing research in the realm of immunology, especially as it relates to the development and course of malignant disease, may in the future be brought to bear more effectively in the treatment of cancer.

CONCLUSION

In closing, I should like to reiterate that the challenge of the field of hypersensitivity today is broad and great. May I urge every individual who

is interested in our specialty to accept this challenge, to lend support to research in this area, and to talk to his patients, friends and associates regarding the potential for progress in this phase of medicine. This approach will help to broaden the concept of physicians and laymen regarding our specialty, will rightly enhance its dignity and will deservedly command greater respect for us among our colleagues in other disciplines.

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SCIENCE AND EXPERIENCE

Lack of experience diminishes our power of thinking and comprehensive view of the admitted facts. Hence, those who dwell in intimate association with Nature and its phenomena grow more and more able to formulate, as the foundation of their theories, principles, such as to admit of a wide and coherent development; while those whom devotion to abstract discussions have rendered them observing to the facts, are too ready to dogmatize on the basis of a few observations.
—ARISTOTLE, 384-322, B.C.

Progress in Allergy

HUMAN ECOLOGY AND SUSCEPTIBILITY TO THE CHEMICAL ENVIRONMENT

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Part I. Background

HOW SAFE is our present chemical environment? To what extent does it contribute to chronic illness? How much do we know about the long-term effects of such by-products of "progress" as the chemical pollutants in the air of our homes and cities; chemical additives and contaminants in our foods, water and biological drugs, as well as our synthetic drugs, cosmetics, and many other personal exposures to and occupational contacts with man-made chemicals?

As new chemicals are constantly being developed for new uses, so-called "safe tolerances" are determined by the results of *animal toxicity studies.* Although checking the response of groups of animals to single substances undoubtedly has protected us from *acute* reactions and reduced *chronic* toxicity in humans, is this enough? Are the results of such chronic toxicity studies to *one specific chemical,* made in *animals* and under ideal laboratory conditions, applicable to *humans* who are daily subjected—often during their lifetime—to *this* chemical and to many *related* chemical exposures? Is not modern man's increasing chemical environment impinging on his health and general welfare?

Since the crux of this problem of man versus man-made chemicals hinges on individual susceptibility and individual adaptation to this environment, several more questions arise. Have animals in the course of these long-term toxicity studies been tested with the excitant under investigation during a phase of adaptation in which reactions on the basis of *individual susceptibility* are accentuated? Or has the occurrence of aberrant responses indicative of individual susceptibility been averaged out? These are *important questions* because the medical problem involved here, in respect to individual susceptibility, is *not* concerned with the *middle* of the distribution curve, but with the *far end!* Whereas acute and chronic toxicity studies of new chemicals in animals are indispensible as *preliminary screening processes,* these should be regarded as a *prelude to observations in man*—especially in susceptibility-prone individuals. Where are these reports? The few that exist tend to involve intermittent exposures and to appear some time *after* the production and distribution of a new chemical has become a "profitable venture."

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Indeed, some of the most troublesome chemical exposures have not been adequately described, and there is no general knowledge of their potential *hazards*. The chief reason for this is that these materials have become integral parts of our current existence. Not being readily avoided accidentally, they are not usually suspected. Not being suspected, they are not usually avoided deliberately. Thus, not being eliminated either by chance or design, certain common chemical exposures remain unsuspected causes of *chronic physical and mental illnesses*. Even though certain chemical exposures may be suspected, avoidance is not only inconvenient and sometimes expensive but, because of the addiction-like responses that may be involved, these exposures often run counter to the desires of certain highly susceptible victims. Thus, observations of individual susceptibility to chemical excitants in humans have been *obstructed* by continuity of exposure and self-perpetuation of the process.

From the material to be presented, it may be said that an *analytic investigation* of the safety of the chemical environment in laboratory animals *has not answered* the above-posed questions. Neither may it be assumed that the observed effects from *controlled* exposures in animals are analogous to the *happenstance* exposures in man. Our analytic investigators seem to have wandered away from the question they set out to solve; the more minutely they have subdivided this problem, the more difficult it is to rejoin its parts. In other words, the sum of the toxicologists' analytical data accruing from animal experiments is *far removed* from the situation confronting humans in their daily lives.

A clinically oriented *synthesis* of the subject is needed. Although a doctor faced by a complaining, chronically sick patient may suspect several chemical exposures, the patient may be reacting to these as well as several *other* unsuspected and related ones. Not knowing the scope of the chemical excitants that might be involved nor how to protect his patient from the potential total of them, the doctor often remains at a loss in handling such a case. Because the totality of the chemical environment and its range of potential clinical effects have not been described, the physician is apt to treat such a patient with *additional* chemically derived drugs, thereby aggravating his problem. Obviously, a broader view and a more fundamentally sound basis of therapy are needed.

HUMAN ECOLOGY

The term *ecology* was first used by Haeckel in 1866[1] in referring to the mutual relations of organisms to their physical conditions of life and to each other, as described by Darwin.[2] Human ecology embodies the concept of a person's adaptation to the conditions of his existence. The ecologic effects of chemical excitants are observed most advantageously by first insulating an individual from the *total chemical environment* and then observing his response to *re-exposure* to previously avoided *parts* of it.[3,4] This

clinically oriented regimen produces an entirely different set of answers to the above questions than currently is supplied by the toxicologists.

The following preliminary summary of the application of this approach in practice may be made:

Chemical excitants—poisons, irritants and various lesser man-made chemical exposures usually regarded as harmless in the dosages encountered—may induce acute or chronic clinical effects, depending principally on dosage and host susceptibility. On one extreme are the acute immediate reactions from massive exposures which are readily apparent and generally harmful to all. Fortunately, we are largely protected from such acute effects by a general knowledge of their harmfulness. On the other extreme are the chronic symptoms traceable to the long-term subtle impingement of frequently encountered lesser exposures to which an ever-increasing minority are apparently becoming susceptible. Unfortunately, we are neither adequately protected from these chronic effects nor generally aware of the potentially noxious nature of such everyday chemical exposures.

Since the biologic problem resulting from exposure to, susceptibility to, and maladaptation to diverse environmental chemical exposures has not been adequately presented from the standpoint of *an individual buffeted by his chemical environment,* this article will attempt to fill that void. In doing so, the writer will draw heavily on his clinical observations during the past two decades. The scope of the subject precludes biographic completeness. This is not a *review* but the presentation of a *point of view* and the program for confronting a common medical problem, previously not recognized satisfactorily and which, heretofore, the writer has only presented preliminarily.[5-8]

ADAPTATION

The body responds to the long-term inurement of environmental excitants in a basically similar manner—that is, by adapting to them. Selye[9,10] described the common features and stages of adaptation to a wide range of materials as the *general adaptation syndrome.* Adolph[11] observed similar stages of adaptation, but found that individual animals not only exhibited marked differences in their responses to the same excitant but also that these manifestations tended to overlap and were more often *specific* to one stressor than general to more than one.

A Clinical Observer's View of Adaptation.—Despite the importance and general dissemination of Selye's views, the basic biologic concepts of adaptation and ecology described by physiologists and other biologists have not been widely applied to the practice of medicine. There seem to be several reasons for this:

1. Traditionally and in contrast to scientists, with the possible exception of pediatricians, physicians have been more concerned with the treat-

ment of individual patients than with observations of the natural course of illness as exhibited by untreated cases.

2. Whereas physiologists have described the sequential stages of adaptation as a I, II, III phenomenon (alarm reaction, stage of resistance, and a stage of exhaustion, respectively), most physicians first see their patients toward the latter part of stage II of adaptation.

In the practice of medicine, one does *not* start with young healthy individuals of uniform age and ancestry who have led previously protected lives, exposing them to regular doses of a given material under controlled conditions and *watch them sicken,* as do physiologists and toxicologists in their animal tests. Doctors ordinarily enter upon the scene when an individual patient is already sick, as a result of a relative exhaustion of a long-term interplay between him and given portions of his environment. It is much as if the physician arrived at the theatre sometime during the last scene of the *second* act of a three-act play—puzzled by what may have happened previously to the principal actor, his patient. To what, how long, and how effectively such a sick person may have been adapting remain unknown. The important point is that the full significance of his adaptation is apt to be missed *unless* an attempt is made to reconstruct earlier stages.

3. As a clinical observer, the writer agrees with Adolph[11] that the combinations and modifications of adaptation in a given person are specific to the excitant. Although Selye[9,10] recognized this possibility, he placed relatively greater emphasis on the general features of adaptation.

4. Lastly, there has been little medical interest in the patient as a whole and his adaptations as an integrated unit to the outside world. This seems to have been due in part to the progressive fractionation of medical practice into specialty subdivisions as well as to the tendency to investigate medical problems by means of a *fractional analysis* of them.

An attempt to synthesize these discordant views held by academicians and clinical observers led the writer to describe the *specific adaptation syndrome.* Since this concept of a person as a functionally integrated unit responding to his environment has been reported only preliminarily,[12] it will be reviewed briefy before describing the chemical environment and its clinical effects.

The Specific Adaptation Syndrome.—Stripped of all interpretations as to mechanisms and stated in simplest terms, the specific adaptation syndrome is a *clinical counterpart* of Selye's general adaptation syndrome. It also consists of merging non-adapted, adapted, and non-adapted developmental stages.

Adaptation is so characteristic of life that an individual usually is oblivious of his adaptive responses to various common materials. Being relatively improved immediately after each specific exposure to which he is adapting, a person may resort to it in an addiction-like manner as often as neces-

sary to remain "picked up." Indeed, this may be the only way he knows to postpone or relieve his otherwise inevitable delayed "hangover-like" reactions, for only thereby does he remain "normal" and without complaints. More commonly, however, such an adapted person simply eats what he likes and does what he is accustomed to do as often as desired without the slightest notion of "adapting" or being involved in any addiction-type of response. Only when one or more of his specific adaptive responses taper off and the stage of exhaustion is approached does he start to complain—a change ordinarily regarded by all concerned as the *onset* of the present illness.

But if *chronic cumulative exposures* to an offending substance acting in this manner are avoided, the following tends to occur: [1] "Hangovers," first accentuated, diminish and disappear as adapted or partially adapted stages (II or III) revert to the initial non-adapted stage (I). [2] Re-exposure to an *isolated dose* of such a previously avoided material then induces an immediate acute reaction which (a) *changes chronic illness to acute illness*, and (b) *demonstrates the causation of many chronic syndromes.* Each subsequent *widely spaced* specific exposure precipitates a similar acute reaction, but with oft-repeated doses, immediate post-exposure effects quickly taper off with the recurrence of a relatively symptom-free, specifically adapted state.

Environmental Factors Eliciting Adapted Responses.—Many go through life adapting to various physical, biologic and chemical environmental materials without apparent ill effects. But in those who happen to become increasingly susceptible, doses ordinarily taken in stride become pathogenic, inducing degrees of maladaptation associated with chronic illness. This concept that chronic disease syndromes commonly result from frequent exposures to environmental substances to which susceptibility exists is *not* widely appreciated in medicine. Consequently, a brief reference to physical and biologic agents inducing adapted and maladapted responses will aid in understanding similar effects attributable to environmental chemicals.

The human race has had millions of years to adjust to cold, light, and other solar radiations as well as various other physical exposures. As a consequence, only a few current specimens become sufficiently susceptible and mal-adapted to manifest symptoms of so-called *physical allergy*. Likewise, most of us are adequately adapted to common foods, plant pollens and oils, spores, insects and other animals. But some become increasingly susceptible to one or more of these common materials and some of this group become chronically sick as a result of *decreasing adaptation* thereto. Similar effects attributable to susceptibility to common chemical exposures currently are not appreciated as major causes of chronic illness. In fact, neither the chemical excitants nor the full range of clinical manifestations resulting therefrom have been adequately described.

Part II. The Chemical Environment, in General

In contrast to these naturally occurring physical and biologic exposures capable of inducing specific susceptibility and manifesting as chronic illness, the man-made chemical environment is a *relatively new* exposure, both racially and individually. Furthermore, whereas the physical and biologic environmental excitants are relatively inert as far as humans are concerned, this is far less true of the chemical excitants to be described. Therefore, and in view of the ever-increasing role of *synthetic chemicals* in our lives, it is not surprising that susceptibility to and maladaptation to this comparatively new and relatively unstable chemical environment is a common major cause of advanced clinical syndromes.

There seems to be several reasons why chemical additives, contaminants, and drugs have not been recognized as common causes of chronic ills:

1. Since a prolonged period of exposure usually precedes the onset of clinical susceptibility and maladaptation to an environmental excitant and since many pathogenic chemicals are relatively new, perhaps sufficient time has not elapsed for the development or the observation of this phenomenon.
2. Another drawback has been the debate as to whether the involved chemicals are *allergens, irritants,* or *toxins;* a difference of opinion that apparently has detracted from the more fundamental facts that specific susceptibility and adaptation are the common denominators of the process. Despite the essential irritant and even toxic nature of some of the agents to be listed, it should be emphasized that the dosages under consideration are not ordinarily regarded as either irritant or toxic.
3. However, the greatest single deterrent to recognizing the causative role of the chemical environment in chronic illness has been the fact that the most effective diagnostic *modus operandi* has not been described.

INCIDENCE

Susceptibility to chemical additives and contaminants of air, food, water, biological drugs and chemically derived drugs has been demonstrated to be the leading factor in the cause of chronic illness in approximately *one-third* of the writer's chronically ill patients. It appears to be a contributing factor which cannot be ignored for best results in the management of *another third.* Other statements concerning the relative incidence of this so-called chemical susceptibility problem cannot be made at this time.

SCOPE

Since this presentation is principally concerned with the factor of *individual susceptibility to the everyday chemical environment,* no attempt will be made to evaluate the effects of toxic or irritant chemical exposures. Neither is this article concerned with the occupational aspects of man's chemical environment other than those peculiar to the household, automobiles, gardens, lawns, and other exposures generally common to the

majority of individuals. Finally, the aim of this report is to emphasize the interrelationships of the chemical problem as a whole rather than to develop particular facets of it. Exceptions will be made for those constituent parts neither adequately recognized nor fully described. For instance, relatively more space will be devoted to the subject of *indoor chemical air pollution* than with drug sensitivity, upon which extensive reports are available.

Awareness of the totality and potential clinical significance of susceptibility to the chemical environment was not apparent until the opportunity of studying several patients who were unusually susceptible to an exceedingly wide range of environmental chemicals. Information gained from such advanced cases since has been applied advantageously to many less advanced instances. Two of these early illustrative cases will be reported in detail, since it is helpful for the reader to understand the possible scope of this problem before taking up individual facets of it. However, it should be emphasized that the methods currently recommended have changed considerably from those employed in working out these early cases.

ILLUSTRATIVE CASE REPORTS

Mrs. N.B., physician's wife and former cosmetics saleswoman, aged forty-one, was first seen in 1947. Since childhood she had been subject to perennial rhinitis, intermittent canker sores, frequent headaches, hives, chronic fatigue, irritability, tenseness, and nervousness. Progressively troublesome coughing and bronchial asthma developed later. Pruritus of her eyelids with edema and circumorbital dermatitis followed each attempt to wear nail polish. She was also highly intolerant to perfumes, certain other scented cosmetics, and many drugs. Chronic depression had become increasingly troublesome.

Although shown to be sensitive to house dust and to silk, a test or therapeutic injection of either—even if infinitesimally small—was followed within fifteen minutes by nasal stuffiness, coughing, and headache. Chocolate, pork, and certain other minor foods were suspected; still others were incriminated on the basis of individual food ingestion tests.[13] But despite avoidance of incriminated materials, she not only remained chronically sick but continued to develop new symptoms and reactions to new materials. Many of her bizarre reports of suspected agents remained unexplained until the development in 1951 of the point of view presented herein.

For instance, each time she came to Chicago she developed acute coughing, asthma and/or headache shortly after entering the extensive petroleum refinery area in Northwestern Indiana, through which she had to pass. She then *remained* sick if quartered on *lower* floors of loop hotels or if she attempted to go about at street level; but she *improved* within twenty-four hours if she remained *above the twentieth floor* in the same area. These responses—markedly accentuated on rainy, humid, foggy or "quiet" days—were subsequently traced to the inhalation of refinery odors in driving into Chicago and to the street-level traffic fumes in the downtown area. Indeed, she had been extremely susceptible to automotive exhausts —especially those from deceleration and diesel engines. If caught behind a diesel truck or bus while driving, she either stopped, passed it, or even violated whatever traffic regulations were necessary to escape from it.

In addition to immediate coughing, asthma, and headache from such exposures, she had been known to develop a state of altered consciousness simulating drunkenness, and a few times had lapsed into an unconscious stupor. Upon three occasions

she had slumped at the wheel while driving in such traffic, an accident having been averted only by another person rescuing the steering wheel. Although she experienced less reaction when riding in the front seat, there were only a few automobiles in which she was able to remain unaffected. Another time, while a front-seat passenger in a car having a defective muffler, she became progressively sick, then stuporous, whereas other passengers neither reported smelling such fumes nor reacted adversely to them.

More recently, this patient's rhinitis and asthma had increased each year, beginning July 4 and extending throughout the summer. This history, not conforming to local hay-fever seasons, finally was traced to the *pine paneling* in her summer home to which she migrated at the *same time* each year. She was also susceptible to the odors of burning pine and various pine-scented materials. She was extremely susceptible to the odors of indoor Christmas trees; evaporating paint containing either turpentine or mineral spirits; laquer, shellac, varnish, and synthetic alcohol.

Upon one occasion she suddenly began to cough and wheeze within a few minutes after entering a hunting lodge which had been heated in advance by means of a fuel-oil stove. This episode remained unexplained until similar heating devices were incriminated under like circumstances. Having previously suspected the odors of her gas kitchen stove and other gas-burning home utilities, sponge rubber padding and upholstery, and certain flexible plastics, these materials had been discarded prior to her initial visit. After the load of her constant chemical exposures had been reduced, she subsequently reported that she reacted to the presence of gas ranges when visiting other homes; also from sitting on sponge rubber or plastic upholstered furniture; from sleeping on sponge rubber mattresses or pillows, or beds in which mattresses and pillows were covered with plastic encasings.

This patient also developed severe respiratory symptoms and headache when filling plastic bags with food for deep freezing, and when she subsequently ate food frozen in plastic, but not from the same food *before* it had been so stored. Similar reactions were observed from eating food which had been stored in plastic refrigerator dishes or which had been stored in open glass dishes in plastic-lined refrigerators, whereas the same *fresh* food or that stored tightly in *glass* was taken without reaction. From this type of experience, she learned the superiority of enamel-lined electric refrigerators.

Since this patient was known to be sensitive to house dust, one might inquire how dust avoidance was handled in view of reactions to the odors of sponge rubber and plastics. One chair which had been treated with Dust Seal (hydrolyzed mineral oil) had to be removed from her home, because she developed respiratory symptoms each time she sat on it. Reactions to injections of *house dust extract* were subsequently traced to *phenol* employed as a preservative. Her problem of house-dust allergy has been handled adequately by general cleanliness, including the frequent cleaning of feather pillows, and injection therapy with phenol-free house dust extracts.

Severe symptoms of the type described, following exposure to perfumes, forced her to give up her work selling cosmetics. Similar symptoms, plus generalized edema and rapid gain in weight, have followed each attempt to wear nylon uniforms, as has contact with certain other synthetic textiles or plastics. Upon three occasions she lapsed into an unconsious stupor immediately after drinking green creme d' menthe. Less severe but similar reactions have also followed ingestion of artificially colored foods: maraschino cherries, mint sauce, frankfurters, bologna, gravies, colored pie and cake frostings and fillings, colored gelatin salads and desserts, ice creams, sherbets, ices, candies, and certain other artificially colored foods and drinks.

Following recognition of the common chemical contaminant factor in these exposures, she inquired why she was able to eat tomatoes from her own garden, whereas commercially canned tomatoes invariably made her sick. Inquiry revealed that she became ill after eating foods canned in *lined tins,* whereas the same *fresh* food or

food packed in *unlined tins* or *glass* did not cause such reaction. Ingestion of commercially available foods containing appreciable quantities of *insecticide spray residues* were followed by similar symptoms, whereas the same home-grown unsprayed foods were taken with impunity.

Originally, she was thought to have been sensitive to beef, on the basis of a positive individual food ingestion test with commercially available beef and similar reactions each time beef was eaten. Later, she found that she *could* eat beef raised on a neighbor's farm—beef which had not been fed commercially processed feeds; beef which had not been sprayed for fly control or injected with antibiotics, and which had been raised on a farm fertilized only with manure. She has since used *this type* of meat without any trouble. Each attempt to re-introduce foods commercially canned in lined tins, foods known to have been sprayed with insecticides, or beef obtained through commercial channels has produced *acute* respiratory symptoms, headache or depression.

A similar reaction was induced by the experimental ingestion of the calculated amount of *coal tar dye* (Amaranth No. 2) which would be found in a large serving of gelatin dessert. She also became sick immediately upon inhaling sulphur odors or drinking heavily sulphured or chlorinated water, eating refined cane or beet sugar, or taking aspirin, saccharine, sulfonamides, barbiturates, methadon, meperidine, and many other synthetically derived drugs.

Treatment of this patient has consisted of avoiding incriminated exposures as detected. Upon one occasion an acute stuporous depression in which she had been unconscious for several hours was treated effectively by the administration of sodium bicarbonate, intravenously. (The use of this will be described subsequently.) Although she had profited by avoiding as many incriminated chemical exposures as possible, the range of materials involved has made complete avoidance exceedingly difficult. In addition, there are certain regular exposures believed to be perpetuating chronic symptoms that have not been avoided. For instance, she is currently addicted to frequent doses of a synthetic drug employed for *pain relief;* also, she is believed to be reacting to the inhalation of fumes arising from the warm air furnace in her home. At least two similarly affected patients—including the following reported case—reacted acutely to the air in this home when visiting there for only one hour during the winter season.

K. S., a housewife, aged forty-four, was first seen in 1953. As a child she usually had a ruddy complexion, was hyperactive and usually ran aimlessly, becoming progressively jittery, irritable and clumsy, with intermittent periods of rhinitis, sick headaches, and car sickness. These symptoms usually were treated with aspirin, bromoseltzer and, later, by antihistaminic drugs. Both chronic and acute effects were accentuated when in the kitchen—where she frequently broke dishes and cried when reproached. She much preferred to remain outdoors where, she said, there was "more air." During her entire childhood she was never able to concentrate or study in her home. Her school work was erratic, there being some good days but many others in which she was unable to remain attentive or to recall what she had previously studied. In retrospect, it appears that the clinical picture was related to homes heated with *unvented kerosene stoves,* illuminated by *kerosene lamps,* and in which cooking was invariably done on *kerosene ranges.*

All symptoms became accentuated upon moving to Chicago at the age of fifteen, and again were heightened immediately after moving into a freshly painted apartment in the fall of 1944. Intermittent colds and bouts of influenza occurred throughout that winter. *Food sensitivity* was suspected for the first time, as evidenced by acute illness after each attempt to eat cherries, although she has since eaten *chemi-*

cally uncontaminated cherries with impunity. The following summer in camp (even though eating *all* foods), she remained entirely symptom-free until the prophylactic administration of sulfonamides, following exposure to scarlet fever. Extreme nausea and listlessness developed immediately.

With the recurrence of rhinitis, bronchitis, and influenza-like symptoms coincident with the onset of cool weather in the fall, she was given sulfonamides a second time. This was followed immediately by the onset of an acute generalized rash necessitating discontinuance of this drug. Severe bronchitis progressed to asthma that autumn while the patient was enrolled in a pottery class. The severity of these respiratory symptoms and the fact that they were accentuated each time she entered the vicinity of the gas-fired pottery kiln necessitated dropping this activity. Throughout that winter she continued with intermittent asthma, unexplained fevers, and extreme fatigue for which she received several courses of antibiotics with little, if any, relief.

During the winter of 1945-46 she was said to have had influenza seven times. Because of almost constant headaches, anorexia, nausea and vomiting she lost 25 pounds in one month. During this time she was receiving daily doses of analgesics and barbiturates—a program followed for the next seven years. Coincident with perennial medications she persisted in having *perennial* rather than *seasonal* symptoms. Although she was suspected of having been sensitive to various drugs, there was little change when these were discontinued, singly. All drug therapy was not stopped simultaneously until 1953. In addition to being sensitive to sulfonamides, by this time she had also become aware of violent reactions to procaine, vitamin B, and certain antibiotics.

Coincident with moving into an old house and painting its interior in the fall of 1947 there was a marked accentuation of her bronchitis and asthma which continued throughout that winter. A major gas leak about the gas kitchen stove was detected toward spring. Finding that she was able to improve her respiratory symptoms temporarily by inhaling the heated air from the gas oven, she repeated this exposure as often as necessary to control her asthma. Although this regimen afforded *immediate temporary* relief of wheezing, it was associated with an increasing level of headaches, staggering gait, depression, and intermittent loss of consciousness. Aching and stiffness of various muscles and joints became so troublesome that she had to be helped from chairs. Most of the three following years she was confined to her bed. During the summer months she improved sufficiently to be outdoors where she seemed to be more comfortable. She also noticed that she was more sick *at her own home* than when visiting in the home of a nearby friend (who happened to have an electric stove in her kitchen). Although this patient had always hated the smell of gas, she had not associated this *daily exposure* with her chronic incapacitating symptoms.

After the usual invalidism through the winter of 1949-50, she was taken to a ranch in the Arizona mountains in April 1950. Within a week she became symptom-free, except for an occasional recurrence of hyperactivity and redness of face followed by headache, severe asthma, and residual myalgia and arthritis. In restrospect, she recalled that these reactions occurred only on colder days when the unvented gas wall heater had been turned on.

Upon returning to her former Illinois home where she continued to use gas utilities for four months that summer she immediately became sick and remained so. That fall she returned to Arizona but moved into an apartment heated by open gas-burning wall units and equipped with a gas kitchen range. Although she remained fairly well when outdoors, indoors she awakened about 3 o'clock each morning with nausea, vomiting, headache, swollen throat, dizziness, ataxia, and severe depression. This persisted until she could again get outdoors into fresh air.

A year later she moved into a ranch-type home having warm air gas central

heating, a gas kitchen range and water heater. In looking back, she claims that she remained sick most of the time here but invariably improved outdoors. This was attributed by those around her to the beneficial effect of sunshine, since she remained miserable when the sun *didn't* shine (and when indoors with her gas utilities).

As her illness progressed, acute episodes became characterized by aphonia, extreme hyperactivity, ataxia, and confusion suggesting alcoholic intoxication. When hospitalized in such a semi-conscious depressed stupor she improved within a few hours and was relatively symptom-free by the third or fourth day; however, she developed a prompt recurrence of symptoms a few hours after returning home. Upon readmission to the hospital she was often accused of having taken dope or having inflicted her acute attacks upon herself in order to return to the hospital. Several such acute episodes were treated by intravenous procaine; this not only failed to help but seemed to prolong the stupor. She was then treated at home by means of attendants, remaining chronically semi-stuporous, confused, and at times hallucinatory. Hearing that she was to be committed to a mental hospital, her brother, a physician, removed her from the state and placed her under the writer's care.

The probable chemical origin of her symptoms was recognized when first seen, although they had not been suspected by the patient or her family. Upon entering an apartment the first night in Chicago she seemed all right, but, coincident with lighting the gas stove to prepare her dinner, she noticed a strong odor of gas and began to feel generally uncomfortable; her eyes and lips burned; face flushed. She became generally excited, ravenously hungry, and complained of a bitter taste in her mouth. Although the stove was turned off immediately and windows were opened, there rapidly developed an increasing hoarseness, aphonia, contracture of the left sternocleidomastoid muscle pulling her head to one side, crossing of eyes, ataxia, mental confusion, and a sense of floating in space.

After a relatively brief span of rapidly increasing hyperactivity and incoordination she slumped into a semi-conscious stupor during which there were brief intermittent wave-like periods in which she could be aroused or could make her wants known but could not speak. She was alternately chilly and excessively warm. Her respiratory rate remained at 20 and her pulse at 73. As the stupor deepened, she developed intermittent fibrillatory muscle twitchings which rapidly progressed to involve larger muscle groups. This manifested as severe muscle cramps in the calves and later throughout the limbs. Continued marked redness of face, extreme air hunger, upward rolling of eyes, progressive opisthotonus and flailing of extremities requiring constant attendance to avoid self-injury—completed the acute picture.

In the absence of additional exposures, the above symptoms leveled off and gradually subsided. Consciousness returned six hours after the onset of this attack, following exposure to a *gas stove* the first time in a week. Her first demand was for water which she drank copiously, but she could not hold the glass. Neither was she able to stand at first; later she was able to walk with assistance, dragging her left foot in a typical ataxic gait. For several hours her left hand was only partially usable. Residual myalgic and arthritic pains persisted for two days; extreme fatigue for another day.

During the following year this patient was observed in many similar attacks, one having been photographed. A report of a neurologic consultation at the inception of the stupor phase is quoted: "Deep reflexes are equal and three-plus; eyes are rolled upward and crossed; she appears to be semi-stuporous but at times responds to spoken voice, at other times not. No response to painful stimuli. Impression: Cataleptic attack. I would strongly suspect hysteria."

Precipitating causes of similar attacks include the following chemical exposures:

1. *Indoor Chemical Air Contaminants:*—Exposure to utility gas or the combustion products of gas, oil or coal—the most troublesome being exhausts from fuel-oil or gas ranges or room heaters, gas refrigerators, gas water heaters and gas driers; coal smoke; warm air heating system odors, irrespective of fuel employed; odors of oil-impregnated filters of air conditioning equipment and evaporating oil from certain other equipment such as motors in electric fans and electric heaters; odors of fresh paint, turpentine, mineral spirits, synthetic alcohol, detergents, household deodorants, disinfectants, Chlorox, ammonia, adhesive cements, sponge-rubber bedding and padding; certain odorous plastics, including upholstery; insecticide sprays, napthalein, dichlorbenzene, and certain other insect repellents.

2. *Outdoor Chemical Air Contaminants:*—Traffic exhausts, industrial air pollution—especially odors arising from refineries and storage tanks; paint manufacture and sulfur processing; insecticide spraying; odors of tarring roofs and roads.

3. *Chemical Additives and Contaminants of Food and Water:*—Foods containing insecticide spray residues, fumigant residues, certain chemical preservatives, sulfur residues, colored chemical flavoring or sweetening agents; foods stored in plastic containers or canned in lined tins; the fats of commercially available beef, lamb, some chicken and other fowl. Drinking chlorinated water or eating food which has been standing in it or cooked in it also causes reactions when otherwise symptom-free.

4. *Synthetic Drugs, Cosmetics and Miscellaneous Chemical Contacts:*—Acute reactions followed the ingestion of acetylsalicylic acid, sulfonamides, synthetic vitamins; injections of procaine as well as epinephrine, allergenic extracts or other biologic materials containing phenol or other chemical preservatives. All cosmetics were suspected except those of biologic origin and free of active synthetic ingredients, scents, colors, and bases. Reactions have been traced to wearing Nylon, Dacron, and certain other synthetic textiles; the use of bed linens washed with detergents, dried in gas driers, or impregnated with plasti-starch also has been incriminated.

MANIFESTATIONS

Since this manuscript is primarily concerned with the description of *chemical environment* and secondarily with the resulting *clinical manifestations,* the latter will be described briefly.

As susceptibility to frequently encountered chemical exposures builds up, the process tends to spread to *related* materials to which exposures also exist. Adaptation to the total load gradually decreases, coincident with the onset of chronic symptoms.

Chronic illness resulting from maladaptation to various parts of the chemical environment may manifest only as eye irritation, rhinitis, burning

of the lips and skin, pruritus, bronchitis, mild gastrointestinal or other relatively minor symptoms, localized principally to major points of contact. For instance, if *smog* is the major exposure, eye irritation, running nose, and coughing may be the principal symptoms, but if spray residues in foods are primarily involved, manifestations may be largely referable to the gastrointestinal tract.

Later, more severe chronic respiratory symptoms may occur, including nasal obstruction, sinus involvement, severe coughing, and bronchial asthma; various dermatoses; a wide range of more troublesome gastrointestinal manifestations, and sometimes urgency and frequency of urination. Mild constitutional symptoms, such as physical and mental fatigue, usually accompany the above chronic localized effects. These most frequently are manifest as fatigue; a cut-back in former energy; lack of initiative and zest for work; forgetfulness; difficulty in thinking, concentrating, and reading comprehension, and sometimes a relative impairment in the sense of humor. Other symptoms which often occur are headaches; various musculoskeletal aching and painful syndromes, including myalgia, fibrositis, bursitis, arthralgia, and arthritis; neuritis and certain other neurologic manifestations; and such other general effects as edema, palpitation, excessive perspiration, pallor, and weakness.

Localized manifestations tend to taper off in the presence of more advanced chronic constitutional syndromes. For instance, there is the chronic level of the so-called "neuroses" characterized by more advanced mental confusion and mild depression. Although manifestations vary considerably, these include a tendency for fixed ideas, one-track thoughts and asocial attitudes; morose, sullen, seclusive, and sometimes hostile and paronoid behavior; negativeness to suggestions; and "dopiness," grogginess, and an indifference to one's surroundings—sometimes approaching lethargy.

Combinations and accentuations of the above symptoms merge with the level of the so-called "psychoses" which are characterized by severe depression, disorientation, regression, and sometimes by hallucinations, delusions, and amnesia. The characteristic alternating tendency of these four levels of chronic "hangover-like" effects, first noted by Savage,[14] has been the subject of a recent report by the writer.[15]

However, if a person is separated from causative environmental exposures perpetuating such chronic "hangover" effects, he tends to improve by retracing these levels of reaction. Although his "hangovers" are first accentuated, he tends to become relatively symptom-free within a few days—the time required depending on the *depth of reaction* and *completeness of the avoidance program.* This changes a partially adapted stage (usually somewhere between stages II and III) to a non-adapted stage I.

Re-exposure to a previously avoided causative excitant to which susceptibility exists now tends to induce an immediate acute reaction which is employed for *diagnostic* purposes, as will be described. The initial "pick up" phase is characterized by *four depths* of *reaction,* which are predominately

motor in type, and a delayed "hangover" phase similar to those previously described, briefly. A given reaction may proceed to any one of these depths before merging with and then being superseded by approximately the same "hangover" level.

Initially, one may become active, alert, and relatively stimulated but otherwise remain symptom-free. This is the stage of response which the *specifically adapted* person often maintains for many months or years as a result of oft-repeated exposures. His lesser grade "hangovers" only manifest themselves at this stage if such a frequently repeated exposure happens to be avoided, but, in such an event, *re-exposure* quickly picks him up again—a status which he comes to regard as "normalcy."

After a time, susceptibility increases, adaptation decreases, and "pick ups" come to be characterized by energetic bursts of physical activity and hyperactivity in which a patient remains nervous, keyed-up, and irritable for several hours. Nearby persons often are involved in inter-personal difficulties that are dubbed "emotional upsets." These, in turn, frequently are interpreted erroneously as "causes" of subsequently developing "hangover" effects.

More intense reactions may occur in which a person is flushed in the face, clumsy, ataxic, argumentative, and aggressive. Here there is an even greater tendency to involve other individuals, but the victim's behavior—so obviously abnormal at this point—is not as apt to be taken seriously by others as in lesser but similar reactions.

Or, there may develop a state of uncontrollable agitation and excitement. This is characterized by rhythmic muscle contractures ranging from muscle twitching to flailing of extremities and epileptiform seizures. Transitory blackouts or more prolonged loss of consciousness may occur. Early "pick up" stages are apt to be compressed into auras or telescoped completely in the initial phase of such rapidly advancing severe reactions. Alternating waves of excessive thirst, voracious appetite and air hunger often typify these "pick up" phases of acute reactions. This may become manifest as eating or drinking binges[16] in earlier phases of reaction, or, in the more advanced stages, by extreme air hunger—a frantic desire for more air or to get outdoors. This may become so intense that a patient will fight any person who interferes with the fulfillment of such overpowering desire.

If a person living at any given "hangover" level is exposed to a substance to which he is susceptible and at least partially adapted, and if the dose is several times *larger* than that to which he is accustomed, he is apt to manifest an acute immediate reaction, becoming relatively stimulated, hyperactive, drunk-like or uncontrollably excited. In general, such a "pick up" occurs at approximately the same depth of reaction as the "hangover" level to which he is ordinarily accustomed, although it may descend a depth lower before returning to its former level. This type of alternation between acute "pick ups" and chronic "hangovers" is epitomized in the most extreme cases by behavior descriptively similar to manic and depressed phases of the

manic-depressive psychosis. Reactions at lesser levels may be simply pictured as *less advanced* responses of similar type. These patterns of reaction, previously described only preliminarily, are being reported *in extenso*.[17,18]

DIAGNOSIS

Susceptibility to the chemical environment is a difficult diagnosis to establish because of the wide individual variations in its manifestations and its potential scope. This is reasonable since no two persons have the same exposures or ability to adapt to them. Indeed, there are valid objections as to whether susceptibility to the chemical environment should be regarded as a *clinical entity*. But the common genesis of the excitants, the general pattern of the response as described, and the tendency for susceptibility to involve an increasing number of facets to which chronic exposures exist, make it desirable to consider the subject in its *totality*.

This common genesis includes the original sources of the hydrocarbons—coal, oil, and gas. If it is permissible to carry the process back another step, and if one accepts the geologic concept that conifer forests were the precursors of these materials, such an interpretation is in keeping with the close association of the clinical effects of *pine and its combustion products* with those of coal, oil, and gas and their combustion products and derivatives.

History.—Although individuals may be aware of susceptibility to one or more of the facets of the constellation of exposures to be described, a chronically ill person rarely ever knows the total number of chemical excitants impinging on his health. Consequently, the history is of only limited value except in the most advanced cases. Owing to its scope, the history is best recorded by means of a questionnaire; this comprehensive one, used by the writer, has not been previously published, except for the incorporation of its early form into the questionnaire employed by Brown and Colombo.[19]

It is suggested that the new patient fill out the questionnaire *before* he becomes acquainted with the scope and possible significance of this problem.

Interpretation of the Questionnaire.—Although there is no single question of paramount importance, the one referring to the ability to *detect escaping gas* deserves special emphasis. Provided a patient has at least an average sense of smell and if he admits of an acute ability to detect the odor of escaping utility gas (as contrasted with others similarly exposed), this suggests *susceptibility* to this aspect of the chemical problem. However, a negative answer to this question, attributable to anosmia, does not rule out susceptibility to indoor chemical air pollution, of which exposure to odors or derivatives of utility gas is the most important constituent. The next most important questions are those dealing with coal smoke, solvent odors, motor exhausts, tar odors, perfumes, scented cosmetics, drugs, and the *first* set of questions concerning *foods*.

In general, it may be said that new patients tend to underestimate the

QUESTIONNAIRE

CHEMICAL ADDITIVES and CONTAMINANTS of AIR, FOOD, WATER, DRUGS & COSMETICS

Date ____ Name _____ Home Address _____

CIRCLE or FILL IN the following: Sex _____ Age _____

Education
Highest school year:
1 2 3 4 5 6 7 8 | 1 2 3 4
Elementary | High
1 2 3 4 | 1 2 3 4
College | Graduate

Marital Status
Single
Married
Widowed
Separated
Divorced

Occupation
Work Region
City
Suburban
Small town
Rural

Work Address
Distance from work _____
Travel by:
Car Train Other _____
Bus Walking _____

Home

Type
Single House
Double House
Apartment
Hotel
Trailer

If multiple dwelling
What floor? _____
How long have you lived there? _____

Region
City residential
City industrial
Suburban
Small town
Rural

Garage
In separate unattached building
With inside passageway between house & garage
In basement of house

Heating & Ventilation of Home

Type
Electric, heat pump
Electric, radiant
Hot water or steam
Warm Air
Space heaters
Fireplaces

Fuel
Electric
Gas
Oil
Coal
Wood
Other ____

Furnace Location
Basement
Main floor
Utility room
Open
Closed

Air Conditioning
Window units
Central system
Filters - oiled,
Unoiled,
Electrostatic
Activated carbon

Kitchen Exhaust Fan
Yes
No

Kitchen Door
Usually left open
Usually closed

Utilities

Range
Electric
Gas
Oil
Age ____

Refrigerator
Type
Electric
Gas
Age _____

Food Storage
In Glass
In enamel ware
In plastic

Deep Freeze
Electric
Gas
Age _____

Clothes Dryer
Electric
Gas
Age _____

Water Heater
Electric
Gas
Part of furnace
Age _____

Furnishings and Household Maintenance

Upholstery Coverings
Cotton Silk
Linen Wool
Synthetic fabrics
Plastic

Padding
Cotton
Hair
Rubber
Other ____

Mattresses
Cotton
Rubber
Plastic covered
Other _____

Pillows
Feather
Rubber
Kapok
Dacron
Plastic covered

Rugs
Wool
Cotton
Synthetic
Natural fiber
Rubber or Plastic backed

Rug Pads
Plastic
Rubber
Hair

Curtains
Cotton silk
Wool linen
Plastic
Synthetic mat.

Cleansers
Soap
Detergents
Scouring pwd. with bleach
Ammonia

Deodorants & Disinfectants
Air wick
Lysol
Pine-Sol
Others _____

Laundry
Soap
Bleaches
Ammonia
Detergents
Plastic starch
Cornstarch
Dryer
Electric
Gas

Furniture Polish
Yes No

Floor Wax
Yes No

(Continued)

significance of the chemical environment as it affects their health. Only those excitants in which the amount per dose or the regularity of dosage are highly variable are apt to be suspected. Moreover, only those persons whose susceptibility is advanced and whose involvement is widespread are apt to indicate that they are "made sick from" these exposures. The majority, *subsequently* found susceptible to major facets of the chemical en-

CHEMICAL ADDITIVES AND CONTAMINANTS -- Continued

Miscellaneous

Insect Control	Drinking Water	Sense of Smell	Ability to Detect Leaking Gas	When Wind is Blowing from Industrial Areas Are your Symptoms Increased Unchanged
Sprays	Spring or well	Very acute	Acute	
Moth Balls	Softened	Normal	Normal or average	
Moth Crystals	Chlorinated	Poor	Poor or absent	
Exterminators	Fluoridated	Absent		

* * * * * * *

WHAT IS YOUR REACTION TO THE FOLLOWING? CHECK ONE:	LIKE	NEU-TRAL	DIS-LIKE	MADE SICK FROM
COAL, OIL, GAS & COMBUSTION PRODUCTS:				
1. Massive outdoor exposures to coal smoke	___	___	___	___
2. Smoke in steam railroad stations, train sheds and yards	___	___	___	___
3. Smoke from coal burning stoves, furnaces or fireplaces	___	___	___	___
4. Odors of natural gas fields	___	___	___	___
5. Odors of escaping utility gas	___	___	___	___
6. Odors of burning utility gas	___	___	___	___
7. Odors of gasoline	___	___	___	___
8. Garage fumes and odors	___	___	___	___
9. Automotive or motor boat exhausts	___	___	___	___
10. Odor of naphtha, cleaning fluids or lighter fluids	___	___	___	___
11. Odor of recently cleaned clothing, upholstery or rugs	___	___	___	___
12. Odor of naphtha-containing soaps	___	___	___	___
13. Odor of nail polish or nail polish remover	___	___	___	___
14. Odor of brass, metal or shoe polishes	___	___	___	___
15. Odor of fresh newspapers	___	___	___	___
16. Odor of kerosene	___	___	___	___
17. Odor of kerosene or fuel-oil burning lamps or stoves	___	___	___	___
18. Odor of kerosene or fuel-oil burning space heaters or furnaces	___	___	___	___
19. Diesel engine fumes from trains, buses, trucks or boats	___	___	___	___
20. Lubricating greases or crude oil	___	___	___	___
21. Fumes from automobiles burning an excessive amount of oil	___	___	___	___
22. Fumes from burning greasy rags	___	___	___	___
23. Odors of smudge pots as road markers or frost inhibitors	___	___	___	___
MINERAL OIL, VASELINE, WAXES, AND COMBUSTION PRODUCTS				
1. Mineral oil as contained in hand lotions and medications	___	___	___	___
2. Mineral oil as a laxative	___	___	___	___
3. Cold cream or face or foundation cream	___	___	___	___
4. Vaseline, petroleum jelly or petrolatum-containing ointments	___	___	___	___
5. Odors of floor, furniture or bowling alley wax	___	___	___	___
6. Odors of glass wax or similar glass cleaners	___	___	___	___
7. Fumes from burning wax candles	___	___	___	___
8. Odors from dry garbage incinerators	___	___	___	___

(Continued)

vironment, most commonly indicate merely a "dislike" when answering this questionnaire. Some of those adapted to one or more of the excitants listed may indicate that they "like" the material in question, especially if they are regularly exposed to it. At least certain patients answering in this manner have been observed to react to an isolated or relatively massive dose of the same material. When a person notices no obvious change upon exposure or

WHAT IS YOUR REACTION TO THE FOLLOWING? CHECK ONE:	LIKE	NEU-TRAL	DIS-LIKE	MADE SICK FROM
ASPHALTS, TARS, RESINS & DYES				
1. Fumes from tarring roofs and roads	___	___	___	___
2. Asphalt pavements in hot weather	___	___	___	___
3. Tar-containing soaps, shampoos and ointments	___	___	___	___
4. Odors of inks, carbon paper, typewriter ribbons & stencils	___	___	___	___
5. Dyes in clothing and shoes	___	___	___	___
6. Dyes in cosmetics (lipstick, mascara, rouge, powder, other)	___	___	___	___
DISINFECTANTS, DEODORANTS & DETERGENTS				
1. Odor of public or household disinfectants and deodorants	___	___	___	___
2. Odor of phenol (carbolic acid) or Lysol	___	___	___	___
3. Phenol-containing lotions or ointments	___	___	___	___
4. Injectable materials containing phenol as a preservative	___	___	___	___
5. Fumes from burning creosote-treated wood (railroad ties)	___	___	___	___
6. Household detergents	___	___	___	___
RUBBER				
1. Odor of rubber or contact with rubber--gloves, elastic in clothing, girdles, brassieres, garters, etc	___	___	___	___
2. Odor of sponge rubber bedding, rug pads, typewriter pads	___	___	___	___
3. Odor of rubber based paint	___	___	___	___
4. Odor of rubber tires, automotive accessories stores, etc.	___	___	___	___
5. Odor of rubber-backed rugs and carpets	___	___	___	___
6. Fumes of burning rubber	___	___	___	___
PLASTICS, SYNTHETIC TEXTILES, FINISHES & ADHESIVES				
1. Odor of or contact with plastic upholstery, table cloths, book covers, pillow covers, shoe bags, hand bags	___	___	___	___
2. Odor of plastic folding doors or interiors of automobiles	___	___	___	___
3. Odor of or contact with plastic spectacle frames, dentures	___	___	___	___
4. Odor of plastic products in department or specialty stores	___	___	___	___
5. Nylon hose and other nylon wearing apparel	___	___	___	___
6. Dacron or Orlon clothing or upholstery	___	___	___	___
7. Rayon or cellulose acetate clothing or upholstery	___	___	___	___
8. Odor of or contact with adhesive tape	___	___	___	___
9. Odor of plastic cements	___	___	___	___
ALCOHOLS, GLYCOLS, ALDEHYDES, ESTERS & DERIVED SUBSTANCES				
1. Odor of rubbing alcohol	___	___	___	___
2. Alcohols or glycols as contained in medications	___	___	___	___
3. Odor of varnish, lacquer or shellac	___	___	___	___

(Continued)

is indifferent to it, he is inclined to answer "neutral" or to leave the question unanswered.

The major use of the questionnaire is to determine whether the patient should be maneuvered in respect to his environment—including the involved part of the diet—in an attempt to demonstrate the existence of susceptibility to aspects of the chemical environment. The more such a questionnaire is used, the greater the latitude in interpreting the significance of how it is answered. For instance, answers and comments that at first

WHAT IS YOUR REACTION TO THE FOLLOWING? CHECK ONE:	LIKE	NEU-TRAL	DIS-LIKE	MADE SICK FROM
ALCOHOLS, GLYCOLS, ALDEHYDES, KETONES, ESTERS & DERIVED SUBSTANCES - Continued				
4. Odor of after shaving lotions, hair tonics or hair oils ...	___	___	___	___
5. Odor ofwindow cleaning fluids ...	___	___	___	___
6. Odor of paint or varnish thinned with mineral solvents	___	___	___	___
7. Odor of banana oil ...	___	___	___	___
8. Odor of scented soap and shampoo ...	___	___	___	___
9. Odor of perfumes and colognes ...	___	___	___	___
10. Odor of Spray Net and other hair dressings ...	___	___	___	___
11. Fumes from burning incense ...	___	___	___	___
MISCELLANEOUS				
1. Air conditioning ...	___	___	___	___
2. Ammonia fumes ...	___	___	___	___
3. Odor of moth balls ...	___	___	___	___
4. Odor of insect repellant candles ...	___	___	___	___
5. Odor of termite extermination treatment ...	___	___	___	___
6. Odor of DDT containing insecticide sprays ...	___	___	___	___
7. Odor of Chlordane, Lindane, Parathione, Dieldrin and other insecticide sprays ...	___	___	___	___
8. Odor of the fruit and vegetable sections of supermarkets ..	___	___	___	___
9. Odor of chlorinated water ...	___	___	___	___
10. Drinking of chlorinated water ...	___	___	___	___
11. Fumes of chlorine gas ...	___	___	___	___
12. Odor of Chlorox and other hypochlorite bleaches ...	___	___	___	___
13. Fumes from sulfur processing plants ...	___	___	___	___
14. Fumes of sulfur dioxide ...	___	___	___	___
PINE				
1. Odor of Christmas trees & other indoor evergreen decorations ...	___	___	___	___
2. Odor of knotty pine interiors ...	___	___	___	___
3. Odor from sanding or working with pine or cedar woods	___	___	___	___
4. Odor of cedar scented furnish polish ...	___	___	___	___
5. Odor of pine scented household deodorants ...	___	___	___	___
6. Odor of pine scented bath oils, shampoos, or soaps ...	___	___	___	___
7. Odor of turpentine or turpentine-containing paints ...	___	___	___	___
8. Fumes from burning pine cones or wood ...	___	___	___	___

(Continued)

glance appear to the doctor to be inconsequential are often highly significant when compared with later demonstrations of causation.

Comprehensive Environmental Control.—Since a history—including an answered questionnaire—cannot be entirely relied upon, and since there are *few* physical and practically *no* laboratory findings that are useful, the diagnosis of the existence of susceptibility to the chemical environment depends principally on observations of a patient as he is *maneuvered* in respect to his *environment.* Since this chemical problem most frequently

CIRCLE CLASSES OF DRUGS, or DRUGS, IF SUSPECTED. NAME OTHERS NOT LISTED.

Analgesics	Adrenalin (epinephrine)	_____
Androgens	Aminophyllin	_____
Anesthetics, local	Aspirin (Bufferin, Empirin)	_____
Anesthetics, general	Barbiturates	_____
Antibiotics	Codeine	_____
Anticoagulants	Demerol	_____
Anticonvulsants	Ephedrine	_____
Antihistaminics	Ether	_____
Antispasmodics	Iodides	_____
Asthma remedies	Mineral Oil	_____
Diuretics	Morphine	_____
Estrogens	Novocaine	_____
Headache remedies	Penicillin	_____
Laxatives	Phenobarbital	_____
Opiates	Phenolphthalein	_____
Sedatives	Saccharine	_____
Steroids	Stilbestriol	_____
Tranquilizers	Sucaryl	_____
Vaccines	Sulfonamides	_____
Vitamins	Vaseline	_____

DRUGS CURRENTLY BEING USED - CIRCLE IF SUSPECTED

_____	_____	_____
_____	_____	_____
_____	_____	_____

Currently used Dentifrice	Currently used Mouthwash	Others
_____	_____	_____

Currently used Cosmetics (Name brands, if possible). Circle if suspected

Deodorant _____	For Women		For Men
Toilet soap _____	Face Powder _____		Electric pre-shave
Shampoo _____	Dusting Powder _____		_____
Hand Lotion _____	Lipstick _____		After shaving lotion
Cold cream _____	Foundation cream _____		_____
Contraceptive _____	Nail polish _____		Hair Oil _____
_____	Perfume _____		_____
_____	Cologne _____		Others _____
_____	Mascara _____		_____
_____	Eyebrow pencil _____		_____
_____	Cold Wave _____		_____
_____	Permanent _____		_____
_____	Hair tint _____		_____
	Douche _____		

(Continued)

coexists with susceptibility to foods, drugs, dust, pollens, and other inhaled particles, the most accurate method of demonstrating the causes of chronic illness is to *observe* the patient while multiple suspected and probable environmental exposures are being avoided, then subsequently returned, one at a time. This technique—soundly based on the principle of changing adapted to non-adapted responses—culminated in the following program of *comprehensive environmental control* and subsequent test re-exposures.[3,4]

Patients are fasted in hospital quarters relatively free of chemical odors

CIRCLE THE FOODS SUSPECTED

1. a) Apple, cherry, peach, apricot, nectarine, pear, plum, olive, currant, persimmon, strawberry, cranberry, raspberry, blueberry, boysenberry, pineapple, rhubarb, grape, orange, grapefruit, lemon, tangerine.

b) Brussels sprouts, broccoli, cauliflower, cabbage, head lettuce, tomato, celery, asparagus, spinach, beet greens, chard, mustard greens, endive, escarole, leaf lettuce, romaine, Chinese cabbage, artichoke.

c) Lamb, beef, pork, chicken, turkey, duck.

2. Dates, figs, shelled nuts, raisins, prunes, other dried fruit; wheat, corn, rye, barley, rice, oats, dried peas, dried beans, lentils.

3. White flour.

4. Peach, apricot, nectarine; fresh apple, fresh apricot, fresh peach, French fried potatoes; molasses, dried fruit, melon, citrus candied peel, fruit marmalade; dried apple, dried pear, dried peach, dried apricot, raisin, prune, corn syrup, corn sugar, cornstarch, corn oil.

5. Creme d' menthe, maraschino cherries, Jello, mint sauce, ice cream, sherbet, hard candy; frostings and fillings of pies and cakes; wieners, bologna, cheese, butter, oleomargarine, orange, sweet potato, Irish potato, root beer, pop, cola drinks.

6. Saccharine, Sucaryl (sodium cyclomate).

7. Banana, orange; apple, pear; coffee; cane sugar, beet sugar.

8. Carrot, parsnip, turnip, tomato, mixed shredded greens; citrus fruit.

9. Rutabaga, parsnip, turnip, green pepper, apple, orange, grapefruit, tangerine, lemon, cucumber, eggplant.

10. Triscuits, cocoanut.

11. Turkey, chicken, duck, eggs, beef, lamb, pork, fish.

12. Chlorinated drinking water; fluoridated drinking water; chlorinated and fluoridated drinking water.

* * * * * * * *

Do you smoke ... cigarettes _____ Pipe _____ Cigars _____
Age you started to smoke _____ Age you last quit smoking _____
Was it difficult to stop? _____ Number of smokes per day _____

What is your maximum weight? _____ Your present weight? _____

and fumes as well as pollens, spores, danders, and dusts. An isolated portion of the hospital devoted to this work is preferred. Indoor air pollution is controlled as far as possible by means of passing incoming air through activated carbon and mechanical and/or electrostatic filters. Patients avoid all drugs, cosmetics, tobacco, and synthetic wearing apparel and drink only spring water.

Symptoms tend to be accentuated at first, usually reaching a peak on the third or fourth day. Chronic manifestations resulting from foods previously

eaten regularly then tend to improve; those from susceptibility to chemical additives and contaminants of foods and those from maintenance doses of synthetic drugs improve more slowly. Chronic reactions from foods *per se* (that is, chemically less contaminated sources) usually start to improve by the fourth day.[16] As might be expected by their previous description, greater depths of chronic "hangovers" subside more slowly than less advanced reactions. Although the average duration of the fast is between five and six days, it is sometimes necessary to continue it for ten days and occasionally longer.

Indications for breaking the fast are a relative absence of or a marked decrease in previous chronic symptoms for a period of at least twenty-four hours; satisfactory sleep, and a stabilization of the pulse rate at a significantly lower level. The fast is usually broken by a meal of unsuspected fish or seafood, chemically uncontaminated insofar as possible. Other foods known not to be significantly contaminated chemically are returned one at a time, preferably not more frequently than twice daily. This routine incorporates the principles of Rinkel's individual food ingestion test[13] and favors the observation of both immediate and delayed objective and subjective effects. Pre- and post-ingestion pulse determinations, as recommended by Coca,[21] aid in interpreting borderline reactions.

After all foods used once in three days, or more frequently, have been tested in this way, susceptibility to chemical additives and contaminants in the diet is investigated. This is done by feeding seldom-eaten foods known to contain chemical additives and/or contaminants in *three daily feedings* for at least *two days.* These foods are selected because of their spray residues and chemical contamination arising from can linings, fumigation, fungicides, sulphur treatment, and other ways to be described; and because of their availability in chemically *uncontaminated* form as *controls.* They consist of canned blueberries sweetened with Sucaryl, canned peaches, canned dark red cherries, canned salmon, canned tuna, frozen broccoli, frozen cauliflower, frozen spinach, raw apple, raw celery, and the outside leaves of head lettuce.

In instances of extreme susceptibility, acute reactions may follow the first ingestion of chemically contaminated foodstuffs, but two days and sometimes longer periods of cumulative ingestion may be necessary before a susceptible person manifests convincing symptoms. At times, the immediate effects of a chemically contaminated diet may be stimulatory. This phase is then followed by the recurrence of any of the localized or constitutional chronic symptom syndromes previously listed.

It is important to emphasize that susceptibility to foods *per se* or to their chemical additives and contaminants may give rise to *identical* symptoms. Although either may occur alone, they most commonly coexist. However, the over-all effects of the chemical additives and contaminants of the diet are apt to be more toxic, cumulative, and associated with greater depths of clinical reaction than ordinarily occurs from susceptibility to foods *per se.*

As soon as the patient and observers are convinced of the presence of acute reactions following test feedings, the gastrointestinal tract is emptied by means of saline laxatives or enemas; these details will be presented subsequently.

Then with the patient on a compatible intake of food and water and avoiding all drugs, he is returned successively to his home, his former water supply, work, and avocations. A recurrence of reactive symptoms during the first forty-eight hours at home usually indicates susceptibility to *indoor chemical air pollutants,* house dust, animal danders, silk, or other home exposures to which susceptibility exists. The most important of these home sources are chemical air pollutants. Details of how these constituent chemical exposures are incriminated will be illustrated by means of case reports after the exposures themselves have been described.

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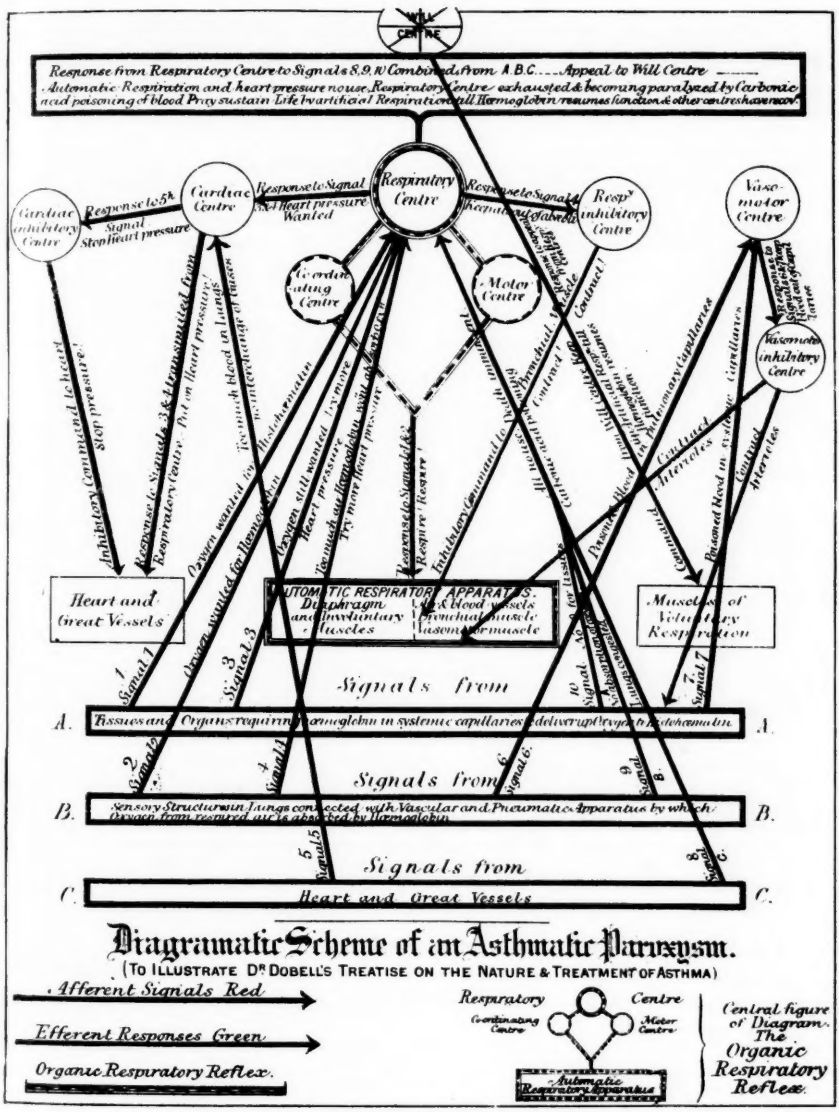
(To be continued)

720 N. Michigan Ave.

DIAGRAMMATIC SCHEME OF AN ASTHMATIC PAROXYSM

Historical Document



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Perlstein, S. M.: The use of fluorometholone (oxylone) in the treatment of various inflammatory and allergic dermatoses. Antibiotic Med., 6:575 (Oct.), 1959.
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Terres, G., and Hughes, W. L.: Acquired immune tolerance in mice to crystalline bovine serum albumin. J. Immunol., 83:459 (Nov.), 1959.
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Matsui, T., and Kuwajima, Y.: Formation of the toxoid of histamine sensitizing factor in Bordetella pertussis. Nature, 184:199 (July 18), 1959.
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Stresemann, E.: The dosage of dexamethasone and triamcinolone in bronchial asthma, Lancet, 2:257 (Sept. 5), 1959.
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Sanders, M., and Nathan, H. A.: Protozoa as pharmacological tools: the antihistamines. Gen. Microbiology, 21:264, 1959.
In ingenious experiments, two protozoa, *Tetrahymena pyriformis* and *Ochromonas malhamensis*, growing in synthetic media, are used for the study of the activity of antihistaminic agents. Growth inhibition and immobilization were noted. Benadryl, Pyribenzamine, and Trimeton were compared with the chemically related procaine. It was noted that L-histidine has some antagonistic effect.

Lawrence, H. S.: Homograft sensitivity: An expression of the immunologic origins and consequences of individuality. Physiol. Rev., 39:811, 1959. Review with 221 references.

Culver, W. E.: Effects of cold on man. An annotated bibliography, 1938-1951. Physiol. Rev., 39 (Supp. No. 3), 1959. (525 pages)

An annotated listing of 2736 references including a chapter on hypersensitivity with 196 references on hypersensitivity.

Exall, L., and Kimbro, P., The mechanism of hemolytic anemia induced by nitrofurantoin (furadantin). (Abs.) Bull. Johns Hopkins Hosp., 101:118 (Aug.) 1957.

A random survey of 296 Negroes disclosed twenty-three sensitive to primaquine (7.8 per cent).

Feldman, P. E.; James, B., and Hildegart, P.: Fatal agranulocytosis during treatment with Pacatal. Am. J. Psychiat., 113:842 (Mar.) 1957; Internat. Med. Dig., 71:88 (Aug.) 1957.

No comment!

Gore, C. P., and Walton, D.: Benactyzine in the treatment of anxiety and tension. Lancet, 2:294 (Aug. 10) 1957.

Thirty-four patients were treated with either a placebo capsule or benactyzine; the dose being 1 mg three times a day for a week and 2 mg three times a day for another three weeks. No differences were noted between the sixteen patients given benactyzine as compared with the eighteen given placebos.

Leopold, H. C., and Leopold, I. H.: Allergic diseases of the eye. Pennsylvania M. J., 60:842 (July) 1957.

Discusses use of Benadryl, epinephrine, cortisone, hydrocortisone, prednisone, and prednisolone. The last four decrease the inflammatory reaction of ocular allergic disorders.

Hartmann, H. A. and Angevine, D. M.: Pseudomembraneous colitis complicating prolonged antibiotic therapy. Am. J. M. Sci., 232:667 (Dec.) 1956; Am. Practitioner, 8:1213 (Aug.) 1957.

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Strahan, E.: The nature of the allergic reaction in the mammalia. M. J. Australia, 2:162 (Aug. 3) 1957.

A comparison and analysis of anaphylaxis as it occurs in mammals. A discussion of the antigen-antibody reaction with support of the arteriolar spasm theory.

Wirth, L.: Prednisolone in iodism—an observation. Military Med., 121:105 (Aug.) 1957.

Prednisolone added to iodoniacin is reported as preventing the appearance of an acneiform eruption in one patient and swelling of the salivary glands in another.

Smith, V. M.: Fatal reactions to penicillin. Evaluation of a test for sensitivity. New Eng. J. Med., 257:447 (Sept.) 1957.

Penicillin anaphylactic reactions caused an estimated 1000 deaths in the United States. A discussion of a simple pre-treatment test.

Callaway, J. Lamar, and Olansky, Sidney: Trimeprazine: an adjuvant in the management of itching dermatoses. North Carolina M. J., 18:320 (Aug.) 1957.

Report on the effectiveness of Trimeprazine given orally to 85 patients with pruritic diseases. Results, including side effects, indicate further use of Trimeprazine and similar agents to control itching.

PAPERS OF INTEREST

McCall, William, Jr., and Pool, Bennette B.: Allergic stomatitis. North Carolina M. J., 18:324 (Aug.) 1957.

A brief summary of etiology, signs and symptoms as well as diagnostic methods and treatments of allergic disease of the oral mucosa.

Hyman, Samuel, and Steigmann, Frederick: Gastrointestinal complications of steroid therapy. Quart. Bull. Northwestern Univ. M. School, 31:213 (fall) 1957.

Review of the mechanism and incidence of gastrointestinal complications in steroid therapy patients. Two cases, with gastric ulcers secondary to steroid therapy, are reported with suggestions of means of prevention.

Editorial: The troublesome staphylococcus. Med. J. Australia, 2:25 (July 6) 1957.

Emphasizes "the intelligent and restrained use of antibiotics, and in particular the conservation of such antibiotics as erythromycin for emergency use."

Light, G. A., Morch, E. T., Engel, R., and Cunningham, J. J.: Promethazine (Phenergan) hydrochloride as an adjunct to anesthesia. J.A.M.A., 164:1648 (Aug. 10) 1957.

Phenergan as a pre-anesthesia medication, when combined with meperidine, with or without chlorpromazine, caused thirteen of twenty-five children to fall asleep, needing no further anesthesia. It was used in 104 patients in all.

Epstein, Isadore S.; Sevag, M. G.; and Brown, F. E.: A simple new procedure for diagnosis of bronchogenic carcinoma. Cancer 9:1075-84 (Nov.-Dec.) 1956.

Based on the higher potassium level of carcinoma cells as obtained by aspiration, a new diagnostic method is described equal in value to the Papanicolaou test.

Steffen, Charles George; Chervin, Max; and Van Vranken, Bruce: Case report—Reactions to mephrobamate. Department of Dermatology, University of Southern California Med., 85:189-91 (Sept.) 1956.

Reactions consisting of vertigo, fever, syncope, erythema, purpura, with an increased lymphocyte and platelet count in the blood are reported as having occurred.

Batson, Jack M.: Anaphylactoid reactions to oral administration of penicillin. New England J. Med., 262:590 (Mar. 24) 1960.

In view of the twenty-six cases of anaphylactoid reactions to orally administered penicillin, discussion of an additional unreported case.

Stein, Myron, Kimbel, Philip, and Johnson, R. L., Jr.: Pulmonary function in hyperthyroidism. Fed. Proc. Am. Soc. Exp. Biol., 99:156, 1958.

There were significant decreases in vital capacity in untreated hyperthyroid subjects, suggesting that dyspnea which is a common symptom in hyperthyroidism without congestive failure is in part due to changes in pulmonary mechanics. These changes were reversible in the seven patients studied.

Lewis, Benjamin M., Lin, Tai-hon, and Noe, Francis E.: Rebreathing method for measurement of pulmonary diffusion capacity. Fed. Proc. Am. Soc. Exp. Biol., 17:95, 1958.

The rebreathing method of Kruhoffer (Acta Physiol. Scand., 32:105, 1954) which utilized radioactive carbon monoxide to measure pulmonary diffusing capacity has been adapted to use stable carbon monoxide.

Speir, Robert S.: Relation of eosinophils to formation of antibody. Fed. Proc. Am. Soc. Exp. Biol., 17:154, 1958.

Studies of eosinophil response to antigen indicate (1) migration of cells to the area of fixation; (2) reaction with antigen; (3) phagocytosis by cells of reticuloendothelial system; (4) proliferation of new eosinophils in bone marrow.

The Shape of Things to Come

Influence of ionic strength of the medium on the anaphylactic sensitization of isolated tissues.
B. N. Halpern and P. Liacopoulos, Nature 187:697 (Aug 20) 1960

Anti-inflammatory drugs and intermediary metabolism.
V. Moses and M. J. H. Smith, Biochem J 78:424 (Feb) 1961

Composition of antibodies against acidic and basic azo-proteins.
Sidney Fleischer et al, Arch Biochem 92:329 (Feb) 1961

Dielectric properties of emulsions. II. Electrical conductivities of O/W emulsions (with 2 figures in 3 details and 1 table).
Hanai Tetsuya, Naokazu Koizum, Takeo Sugano and Rempei Gotoh, Koloid Zeitschrift 171:20 (July) 1960

Some properties of human anti-antibody.
J. S. Beck, Brit J Exp Path 52:7 (Feb) 1961

Studies on ultrasonic emulsification.
R. S. Krishnan. V. S. Venkatasubramanian and E. S. Rajagopal, J Coll Sci 16:41 (February) 1961

Antihistamine activity of extracts prepared from buffy-coat layer of horse blood and from oak gall.
W. Feldberg and B. A. Kovacs, J Physiol 154:461 (Dec) 1960

Enzymic oxidation of 5-hydroxytryptamine by pig serum.
H. Blaschko and W. G. Levine, J Physiol 154:599 (Dec) 1960

Inhalation and skin test in asthmatic children.
J. Kaude, Helv Paediat Acta 15:580 (Dec) 1960

The immunological theory of cancer.
H. N. Green, Unio Internationalis Contra Cancrum Acta 17:215, 1961

Immunological components of carcinogenesis.
M. Feldman, Unio Internationalis Contra Cancrum Acta 17:234, 1961

The toxic effects of penicillin and other antibiotics in guinea pigs.
E. Effenberger and H. P. R. Seeliger, Arzneimittel-Forsch 11:38-41 (Jan) 1961

Experimental autoanaphylaxis.
E. L. Nelson, R. S. Berk and W. A. Krotoski, Bact Proc (Apr) 1961

The effects of adjuvants on antibody production against staphyloccocus toxoids.
L. J. Griffith and W. E. Ostrander, Bact Proc (Apr) 1961.

Fluorescent antibody detection of influenza virus in trypsis-elastase dispersed chick embryo. lung cultures.
R. F. Gilfillan, Bact Proc (Apr) 1961

Automatic screening of normal and abnormal electrocardiograms by means of a digital electronic computer.
H. V. Pipberger. R. J. Arms and F. W. Stallmann, Proc Soc Exp Biol Med 106:130 (Jan) 1961

A study of the formation of antibodies in new-born animals following transfer of nucleoprotein fractions.
Hrubesova Miroslava, Folia Microbiol 6:55 (Jan) 1961

The formation of histamine in the rat.
J. M. Telford and G. B. West, J Pharm Pharmacol 13:75 (Feb) 1961.

Energy metabolic aspect of histamine release in anaphylaxis.
Hidemasa Yamasaki, Saburo Muraoka and Koiti Endo, Jap J Pharmacol 10:21 (Sept) 1960

Effect of a histamine liberator and of serotonin on plasma pepsinogen in rats.
K. Kowalewski, Arch Int Pharmocodyn 139:71 (Dec) 1960

News Items

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE

The annual meeting of the American Association for the Study of Headache will be held at the Park Sheraton Hotel on Sunday, June 25. The meeting begins at 9:00 A.M. A round-table discussion will be one of the features of interest.

SOUTHEASTERN ALLERGY ASSOCIATION

The annual meeting of the Southeastern Allergy Association will be held in Charlottesville, Virginia, at the Thomas Jefferson Inn on October 21, 1961. This year, the meeting will last for only one day because of the Fourth International Congress of Allergology which will be held in New York from October 15 through October 20.

Dr. John Guerrant, University Hospital, Charlottesville, Virginia, is the chairman of the program, and those who wish to present a paper should communicate with him.

EUROPEAN ACADEMY OF ALLERGY

At a recent meeting in London, the European Academy of Allergy elected the following officers:

President	Dr. D. A. Williams
Vice-President	Prof. U. Serafini
President-elect	Dr. E. Bruun
Secretary General	Dr. W. J. Quarles Van Ufford
Treasurer	Dr. J. Jamar
Secretary	Dr. S. Kraepelien

HYPNOSIS WORKSHOP

"Pain, Pain Control, and Symptom Removal" will be the theme of a full day Workshop to be conducted by the Institute for Research in Hypnosis. The sessions will be held at the Sheraton Hotel, Cleveland, Ohio, on October 3, 1961, in conjunction with the annual meeting of the Society for Clinical and Experimental Hypnosis. The fee is $50.00.

BOOK REVIEWS

PHARMACOLOGY. THE NATURE, ACTION AND USE OF DRUGS. Harry Beckman, M.D. Philadelphia: W. B. Saunders Company, 1961. 805 pages. Price, $15.50.

Few reviewers could improve on Beckman's inimitable style. The following paragraphs are chosen from his first chapter, entitled "A Justification of Pharmacology and Pharmacologists." They do more than a dry-as-dust list of chapter headings, which after all can either deal, as they so often do, with groups of drugs or with organs and systems and how drugs affect them. Beckman's is the second choice.

"I imagine that no one who is not a devotee of some absurd cult would think of questioning the worth of the knowledge accumulated in the anatomic, biochemical, physiologic and pathologic fields in modern times or of requiring the scientists engaged therein to justify their procedures and scientific behavior. It is not unlikely, however, that you will begin wondering about pharmacology and pharmacologists before you have advanced very far in your initial acquaintance with this discipline, . . ."

"In physiology, biochemistry, anatomy and pathology you became acquainted with the modern version of the oldest quest in mankind's history, the desire to learn what constitutes life. What differentiates life from death? What is it to be alive that, not being, is death? And the men and women you met in the laboratories where pursuit of the answers to these questions is made were busily codifying observed facts and, whenever progress warranted, offering explanations. Exaggeration of the importance of this work would be impossible, and the stature of some of those engaged in it, past and present, is really gigantic."

"All these things we know, and many more, and it is wonderfully reassuring that we do. The patterns are becoming familiar, life's mysterious veils are parting; Nature's stalwart ways, and even some of her cuter little tricks, are being revealed."

"Yes, we have learned much of how the thing is done *naturally*, but there are some of us whom this does not completely satisfy, rather impish fellows, I am afraid, who feel that this is all very well, necessary knowledge and all that sort of thing, but what has man had to do with its first causes. These ways of being, in whose rules and regulations the biochemists and others have become so expert, were developed quite independently of any aid from man or woman, chick or child. Now what, we ask, will happen if we ourselves take a hand and try to make things work just a bit differently, function slightly at least according to our own desires? What if we were to tinker? Would outcomes be changed? We ask, 'May we interfere?' and, being pharmacologists and therefore bold as bold, we do so at once without awaiting Nature's permission."

"Of course this is impertinence of a very crass order, and I imagine you will consequently expect to find a certain upstartishness in the pharmacology laboratory, but it really is not there. The cry of 'wonder drug' goes up upon occasion, to be sure, but most of us who have grown long of tooth in these endeavors know how to take such things in our stride. Actually, we feel ourselves neither forward nor particularly ultramodern in messing up with our drugs the orderly processes of nature. Our kind of people have been at this sort of thing for so very long that disruption no longer dismays us. Indeed the title, 'pharmacologists,' by which we are currently known, is actually only the most recently applied venerable list extending back into the dim days antedating written history. Some may cavil, but I think we are no more than the spiritual descendants of the witch doctors and medicine men of a more primitive period. For, in their time and according to their capacities, they sought to do precisely what we, in our own age with all its attendant advantages, are striving to achieve—to upset the course of things in behalf of a single individual when all the forces of Nature are pitted against both him and us!"

But pharmacology is fun, and being a pharmacologist is a good life with no chance of it ever becoming dull. I hope to convince you in the pages of this book that the science is making contributions to medicine of which every one of us has sound reason to be quite proud."—E.A.B.

BOOK REVIEWS

DER SCHNUPFEN (Coryza). Prof. Eigler and D. G. R. Findeisen, Editors. Second Edition, 164 pages, 24 illustrations, Leipzig: J. A. Barth, 1960 (In German).

This small monograph covers the etiology, pathology, diagnosis and treatment of coryza. It generally restricts itself to an outline of the questions involved although there is considerable overlapping within the individual chapters. Speculation often takes precedence over established evidence. Particularly concerning therapeutic procedure, each contributor was free to expound his special ideas without much effort to provide evidence for the efficacy of his recommendations. Although allergic conditions occupy a prominent place, there are no details on testing and on desensitization procedure.

This reviewer found two topics of considerable interest: The diagnostic considerations concerning the clinical differentiation of corzya according to causation (infectious—allergic—reflectory) by E. Fuchs and the chapter on occupational rhinitis by H. A. E. van Dishoeck.

A.J.W.

INDIVIDUALITY

Individuality seems to be a basic tenet of science as well as of democracy.

In a recent nineteen-day University of Texas test, a group of "uniform" white rats was allowed to select food, drink and exercise.

It turned out that one rat ate seven times more butter than another; one ate seventeen times more sugar than another; one drank fifteen times more alcohol than another; one ate forty-five times more fortified yeast than another; one excreted ten times more urine than another; one excreted ten times more phosphate in urine than another (in this case, both were on the same diet!); one traveled the equivalent of 150 feet a day while another averaged a whopping *six miles.*

If supposedly uniform experimental rats vary as much as this, how much more important is biochemical individuality in the life processes of human beings, with their far more diversed genetics. Long live the individual!—HARRY M. SCHWALB, *The Laboratory,* 29:31 (Feb) 1961.